Title Page

Protocol Title:
CoolSculpting® Elite: Multi-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen, Flanks, Upper Arms, Inner Thighs, Outer Thighs and Submental Area [redacted]

Protocol Number:
MED-MA-PLS-0647

Investigational Product:
CoolSculpting® Elite

Study Phase:
Post-marketing

Sponsor Name and Legal Registered Address:

Allergan Aesthetics, an AbbVie Company
2525 Dupont Drive
Irvine, CA 92612
USA

Allergan Ltd.
Marlow International
Parkway, Marlow, Buckinghamshire SL7 1YL
United Kingdom

Manufacturer:
ZELTIQ Aesthetics, Inc.
4410 Rosewood Drive
Pleasanton, CA 94588
USA

Allergan Device Medical Safety Physician Contact Information:
[redacted]
Allergan plc
95 Corporate Drive
Bridgewater, NJ 08807, USA
Tel (office): [redacted]
Email: [redacted]

SAE Reporting Email:
For US and All other countries outside EU: LC-Medical_Safety@Allergan.com
For EU: DL-LC-Global_Safety_Reporting@Allergan.com

Sponsor Signatory:
[redacted]
Director, Medical Affairs
U.S. Body Contouring
Allergan Aesthetics, an AbbVie Company
Refer to the Protocol Approval Signature section of this protocol for electronic signature and date of approval.

Table of Contents

List of Tables

List of Figures

Protocol Approval Signature

Protocol Title: CoolSculpting® Elite: Multi-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen, Flanks, Upper Arms, Inner Thighs, Outer Thighs, and Submental Area [redacted]

Protocol Number: MED-MA-PLS-0647

This study will be conducted in compliance with the clinical study protocol (and any amendment[s], if applicable), ISO 14155(2011), guidelines for current GCP and applicable regulatory requirements.

Sponsor Signatory

[redacted]
Director, Medical Affairs
U.S. Body Contouring
Allergan Aesthetics, an AbbVie Company
2525 Dupont Drive
Irvine, CA 92612
USA

[redacted]

1. Protocol Summary

1.1. Synopsis

Protocol Title: CoolSculpting® Elite: Multi-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen, Flanks, Upper Arms, Inner Thighs, Outer Thighs and Submental Area [redacted]

Short Title: CoolSculpting Elite for Non-Invasive Fat Reduction

Rationale: The purpose of this trial is to further evaluate the safety, effectiveness, and patient satisfaction with the redesigned dual applicator CoolSculpting Elite System when cryolipolysis treatments are applied simultaneously or sequentially for non-invasive subcutaneous fat reduction of the abdomen and flanks, upper arms, submental area, inner thighs, and/or outer thighs. In addition, patient reported outcome (PRO) instruments were developed to better assess overall patient satisfaction.

Objectives and Measures

Objectives	Measures
To evaluate participant satisfaction and effectiveness of the CoolSculpting Elite System using CoolSculpting Elite applicators for non-invasive subcutaneous fat reduction of the abdomen and flanks, upper arms, inner thighs, outer thighs and submental area	• Cryolipolysis Satisfaction Questionnaire (CSQ)-Midsection (abdomen and flanks) • CSQ-Overall (if additional body area(s) beyond abdomen and flanks are treated) • CSQ for individual additional body areas treated (upper arms, inner thighs, outer thighs, submental area) • Cryolipolysis General Procedure Questionnaire (CGPQ) • Cryolipolysis Psychosocial Impact Questionnaire (CPIQ) • Participant Evaluation of Noticeable Improvement • Photography and independent photography review (IPR) • 3D (three-dimensional) imaging of change in volume of fat
To evaluate safety of the CoolSculpting Elite System using CoolSculpting Elite applicators for non-invasive subcutaneous fat reduction of the abdomen and flanks, upper arms, inner thighs, outer thighs and submental area	• Adverse events (AEs) and adverse device effects (ADEs); serious adverse events (SAEs), serious adverse device effects (SADEs) • Unanticipated AEs or SAEs (previously unknown to the device) • Pain assessment

Overall Design

Disclosure Statement: This is a multicenter, multi-country, prospective, open-label, nonrandomized, interventional cohort, medical device post-marketing study evaluating the use of CoolSculpting Elite and CoolSculpting Elite applicators for noninvasive subcutaneous fat reduction of the abdomen, flanks, upper arms, inner thighs, outer thighs, and submental area in healthy volunteers.

Number of Participants: Approximately 110 participants will be enrolled and approximately 96 participants are expected to complete the primary endpoint assessment based on an anticipated attrition rate of 12% or less.

The effectiveness measures are the CSQ for midsection (abdomen and flanks) and other treated body areas, the CGPQ, the CPIQ, Participant Evaluation of Noticeable Improvement, photography with IPR, and 3D Imaging.

The primary effectiveness endpoint is the proportion of participants who report being "satisfied" or "very satisfied" on item 1 for the CSQ-Midsection, measured at Week 12 (Visit 8) for participants who receive 1 treatment session, or at Week 20 (Visit 9) for participants who receive 2 treatment sessions.

Intervention Groups and Duration: All participants 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.

Participants are eligible to receive up to two treatment sessions separated 8 weeks apart for the body areas eligible for treatment. Assessments will be completed 12 weeks after the final treatment session.

- If a participant receives only one treatment session for specific body area(s), the participant will return at Visit 8 for the 12-week post-treatment session 1 follow-up assessment and study exit.
- If a participant receives two treatment sessions for specific body area(s), the participant will return at Visit 9 for the 12-week post-treatment session 2 follow-up assessment and study exit.
- If a participant receives only one treatment session to a specific body area and two treatment sessions to another specific body area, the participant will return for both 12-week follow-up visits: Visit 8 for the 12-week post-treatment session 1 assessment of the body area that received only one treatment session and Visit 9 for the 12-week post treatment session 2 assessment of the body area receiving two treatment sessions; Visit 9 will also be the study exit visit for this participant.

Participant body areas selected for treatment during the study must be treated during the first treatment visit (Visit 2) and no new body areas may be treated at Visit 6. Participants planning to receive only one treatment session to a specific body area must have this treatment in Visit 2 during the first treatment session. Per investigator discretion, body areas identified for treatment may be treated simultaneously or sequentially. If sequential or simultaneous treatment is performed, there will be no difference in other treatment activities. Skin preparation, pain assessment, treatment site assessment, and post-massage, etc. will be identical in either case.

The study duration is up to approximately 20 weeks and consists of up to 7 scheduled study visits and 2 phone follow-ups per participant:

- Visit 1 (screening, Days -7 to 1)
- Visit 2 (treatment session #1, Day 1 + 3 days)

  Note: Treatment plan may be completed within a 7-day window from the day when the initial treatment is administered for this visit. The entire treatment session #1 plan for all the body areas selected for treatment must be completed within these 7 days.
- Visit 3 (1-week phone follow-up from last treatment day for participants who received treatment session #1 on any body area)

  Note: If any of the following local effects of erythema, bruising, swelling, and/or sensory alteration are reported during Visit 3, additional phone follow-up (or in-person visit if aligned to planned study visit) will be scheduled in accordance with the time criteria outlined in Table 2-1 for potential AE categorization.
- Visit 4 (4-week follow-up after treatment session #1, Day 28 + 10 days)
- Visit 5 (8-week follow-up after treatment session #1, Day 56 + 14 days)
- Visit 6 (treatment session #2 [optional], Day 56 + 14 days, can be completed on the same day as Visit 5)

  Note: Only body area(s) that were treated at Visit 2 and that require a second treatment session are to be treated at Visit 6. The treatment plan for specific body area(s) may be completed within a 7-day window from when the initial treatment is administered for this visit. The entire treatment session #2 plan for the body area(s) selected for a second treatment must be completed within these 7 days.
- Visit 7 (1-week phone follow-up from last treatment day for participants who received treatment session #2 on any body area)

  Note: If any of the following local effects of erythema, bruising, swelling, and/or sensory alteration are reported during this Visit, additional phone follow-up (or in-person visit if aligned to planned study visit) will be scheduled in accordance with the time criteria outlined in Table 2-1 for potential AE categorization.
- Visit 8 (12-week follow-up/exit for participants with any body area that underwent only treatment session 1 at Visit 2, Day 84 + 14 days). If the participant receives only one treatment session to all body areas, this visit is also the study exit visit.

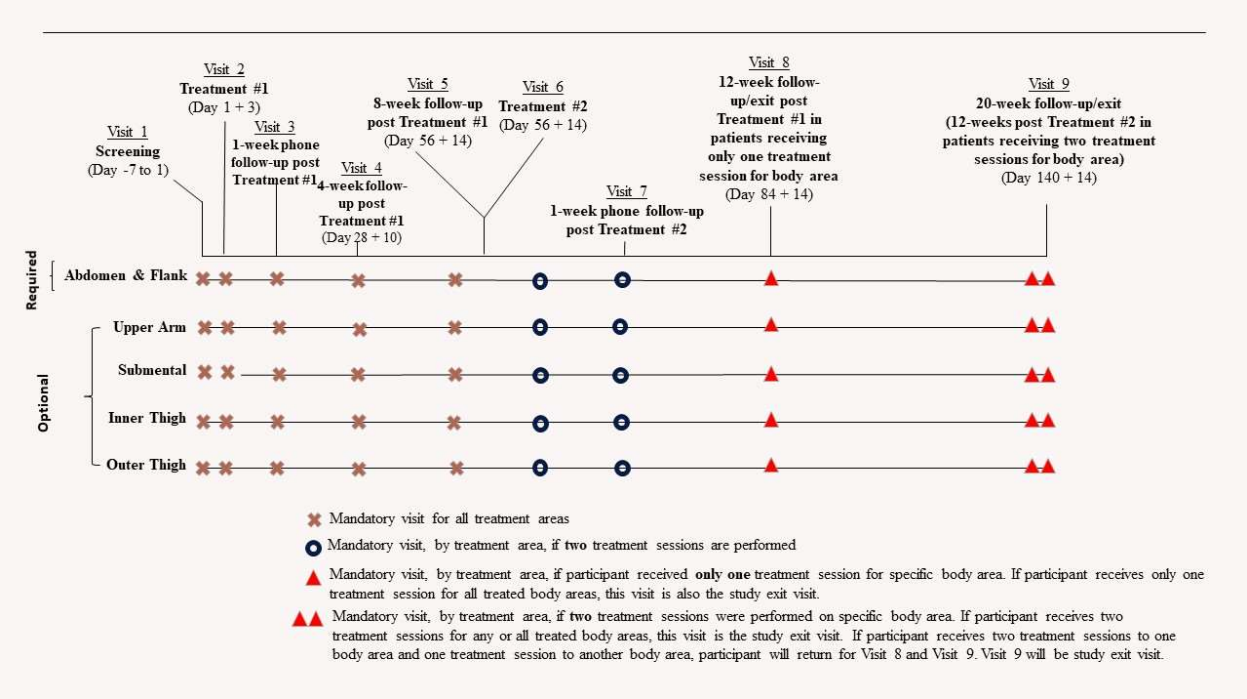
  Note: If the participant receives only one treatment session to a specific body area and two treatment sessions to another specific body area, the body area that received only one treatment session will be assessed at this visit. The participant will return at Visit 9 for assessment of body area that received two treatment sessions and study exit.
- Visit 9 (20-week follow-up/exit, corresponding to 12-week follow up for participants with any body area that underwent treatment session 2 at Visit 6, Day 140 + 14 days). If the participant receives two treatment sessions to any or all treated body areas, this visit is also the study exit visit.

During the course of the study, should it ever become necessary to remain isolated at home or to shelter-in-place per local, regional, or state pandemic-related orders, the sponsor will engage with study site staff in efforts to ensure the safety of participants, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage participant continuity of care. This may include alternative methods for assessments (eg, phone contacts or virtual site visits) in agreement with the sponsor. In all cases, these alternative measures must be allowed by local regulations and permitted by the Independent Review Board (IRB)/Independent Ethics Committee (IEC). Investigators should notify the sponsor if any urgent safety measures are taken to protect the participants against any immediate hazard.

1.2. Schema

The study schema is presented in Figure 1-1.

Figure 1-1 Study Schema



The SoA is presented in Table 1-1.Study procedures are recommended to be done in sequence as listed in the below schedule.

Table 1-1 Schedule of Activities

Evaluations	Visit 1 Screening	Visit 2 Treatment Session #1	Visit 3 1-week Phone Follow-up [1a,b]	Visit 4 4-week Follow-up	Visit 5 8-week Follow-up	Visit 6 Treatment Session #2	Visit 7 1-week Phone Follow-up[2a,b]	Visit 8 12-week Follow-up/Exit for participants who received only 1 treatment session[3]	Visit 9 20-week (12-week Follow-up/ Exit for participants who received 2 treatment sessions)[3]	Notes
Visit Window	**Day -7 to 1**	**Day 1 + 3**		**Day 28 + 10**	**Day 56 + 14**	**Day 56 + 14**		**Day 84 + 14**	**Day 140 + 14**	
Visit Notes	**Mandatory** for all treatment areas	**Mandatory** for all treatment areas	**Mandatory** for all treatment areas	**Mandatory** for all treatment areas	**Mandatory** for all treatment areas.	**Mandatory**, by treatment area, if **two** treatment sessions. May occur same day as Visit 5.	**Mandatory**, by treatment area, if **two** treatment sessions	**Mandatory**, by treatment area, if **only one** treatment session	**Mandatory**, by treatment area, if **two** treatment sessions	See Section 7.2 for detail on information to be captured in Visit in case of study discontinuation
Informed Consent	X									
Inclusion/ Exclusion	X	X		X	X	X		X	X	See Sections 5.1 and 5.2
Demographics	X									
Medical/ Surgical History	X									
Concomitant Medications and procedures	X	X	X	X	X	X	X	X	X	See Section 6.5.1. At Visits 2 and 6, repeat if participant is treated over multiple days with > 24 hours between treatments.
Review Contraceptive Guidance	X	X	X	X	X	X	X	X	X	See Section 10.4, for WOCBP

Evaluations	Visit 1 Screening	Visit 2 Treatment Session #1	Visit 3 1-week Phone Follow-up [1a,b]	Visit 4 4-week Follow-up	Visit 5 8-week Follow-up	Visit 6 Treatment Session #2	Visit 7 1-week Phone Follow-up[2a,b]	Visit 8 12-week Follow-up/Exit for participants who received only 1 treatment session[3]	Visit 9 20-week (12-week Follow-up/ Exit for participants who received 2 treatment sessions)[3]	Notes
Urine Pregnancy Test	X	X				X				See Section 8.2.3, conduct before cryo-lipolysis treatments at Visits 2 and 6. At Visits 2 and 6, repeat if participant is treated over multiple days with > 24 hours between treatments.
Treatment site assessment		X		X	X	X		X	X	Conduct after cryo-lipolysis treatments and prior to massage at Visits 2 and 6.
Height	X									
Weight	X	X		X	X			X	X	Conduct before cryo-lipolysis treatments at Visits 2 and 6.
2D/3D Photography[4]	X	X		X	X			X	X	See Section 8.1.2, conduct before cryo-lipolysis treatment at Visits 2 and 6
Cryolipolysis Treatment		X				X				See Section 6
Pain Assessment		X	X	X	X	X	X	X	X	See Section 8.2.1

Evaluations	Visit 1 Screening	Visit 2 Treatment Session #1	Visit 3 1-week Phone Follow-up [1a,b]	Visit 4 4-week Follow-up	Visit 5 8-week Follow-up	Visit 6 Treatment Session #2	Visit 7 1-week Phone Follow-up[2a,b]	Visit 8 12-week Follow-up/Exit for participants who received only 1 treatment session[3]	Visit 9 20-week (12-week Follow-up/ Exit for participants who received 2 treatment sessions)[3]	Notes
AE, SAE, ADE, SADE	X	X	X	X	X	X	X	X	X	At Visits 2 and 6, repeat if participant is treated over multiple days with > 24 hours between treatments.
Device Complaint Query		X	X	X	X	X	X	X	X	At Visits 2 and 6, repeat if participant is treated over multiple days with > 24 hours between treatments.
CSQ [6 versions][5]					X			X	X	See Section 10.6-10.11
CGPQ[6]								X	X	See Section 10.12
CPIQ[7]		X			X			X	X	See Section 10.13 Complete before cryolipolysis treatment at Visit 2.
Participant Evaluation of Noticeable Improvement				X						See Section 10.15
[redacted]								X	X	[redacted]

[1a] Phone follow-up should be scheduled 7 days from last treatment visit day in instance where participant received treatment session #1 over multiple days.

[1b] If, during this phone follow-up, any of the following local effects of erythema, bruising, swelling, and/or sensory alteration are reported related to treatment session #1, additional phone follow-up (or in-person visit if aligned to planned study visit) will be scheduled in accordance with the time criteria outlined in Table 2-1 for potential AE categorization.

[2a] Phone follow-up should be scheduled 7 days from last treatment visit day in instance where participant received treatment session #2 over multiple days.

[2b] If, during this phone follow-up, any of the following local effects of erythema, bruising, swelling, and/or sensory alteration are reported related to treatment session #2, additional phone follow-up (or in-person visit if aligned to planned study visit) will be scheduled in accordance with the time criteria outlined in Table 2-1 for potential AE categorization.

[3] If a participant receives only one treatment session for specific body area(s), the participant will return at Visit 8 for the 12-week post-treatment session #1 follow up assessment and study exit. If a participant receives two treatment sessions to any or all treated body areas, participant will return at Visit 9 for 12-week post-treatment session #2 follow-up and study exit. If a participant receives only one treatment session to one specific body area and two treatment sessions to another specific body area, the participant will return for Visit 8 for 12-week follow-up for the body area that received only one treatment session and Visit 9 for 12-week follow-up of body area that received two treatment sessions. The exit for this participant is Visit 9.

[4] For select study sites with 3D camera system, 3D images will also be taken at this time.

[5] CSQ-Overall is to be administered only if patient received treatment to midsection (abdomen and flank) plus at least one additional specific body area. The CSQ-Overall should be completed at visit where at least 12-weeks have passed since the final treatment session for all the treated body areas. For example, if the participant receives only one treatment session for one specific body area but two treatment sessions for another specific body area, the CSQ-Overall should be administered at Visit 9 where all the treated areas will have undergone at least a 12-week post treatment period.

[6] The CGPQ should be completed at visit where at least 12-weeks have passed since the final treatment session for all the treated body areas. For example, if the participant receives only one treatment session for one specific body area but two treatment sessions for another specific body area, the CGPQ should be administered at Visit 9 where all the treated areas will have undergone at least a 12-week post treatment period.

[7] The 12-week post final treatment CPIQ should be completed at visit where at least 12-weeks have passed since the final treatment session for all the treated body areas. For example, if the participant receives only one treatment session for one specific body area but two treatment sessions for another specific body area, the CPIQ should be administered at Visit 9 where all the treated areas will have undergone at least a 12-week post treatment period.

Should it ever become necessary to remain isolated at home or to shelter-in-place per local, regional, or state orders, study visits may be impacted. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided throughout Section 8. Every effort should be made to ensure the safety of participants and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic or natural disaster-related reasons, follow the modifications provided throughout Section 8.

2. Introduction

The sponsor is investigating non-invasive subcutaneous fat reduction of the midsection (abdomen and flanks), upper arms, inner thighs, outer thighs, and submental area utilizing the CoolSculpting® Elite System with CoolSculpting® Elite applicators.

2.1. Study Rationale

The CoolSculpting device and applicators have been redesigned and updated (now known as CoolSculpting Elite) and therefore warrant further clinical investigation. While the technological characteristics and operating principals associated with the treatment remain unchanged from the predicate CoolSculpting device, the system has been enhanced to support the simultaneous use of two applicators, improving overall treatment efficiency. This innovation is reflective of physician feedback that suggests patients would prefer to have multiple treatment cycles performed at once rather than serial treatments in order to reduce the overall time of procedure and office visits. In addition, there is minimal data evaluating CoolSculpting treatment across multiple body areas that also captures patient satisfaction and treatment experience. This approach is reflective of real-world experience, where patients may be assessed for treatment on multiple body regions depending on areas of interest for noninvasive fat reduction. This study will collect meaningful data for the use of the CoolSculpting Elite system and CoolSculpting Elite applicators. [redacted]. The purpose of the study described here is thus to further evaluate the safety, effectiveness, and patient satisfaction with the CoolSculpting Elite System in a more robust population and at both US and International sites. With the CoolSculpting Elite system, treatment applicators can be applied simultaneously while undergoing non-invasive subcutaneous fat reduction of the abdomen and flanks, upper arms, submental area, inner thighs, and/or outer thighs. The full applicator range will be utilized as applicable and per country clearances. In addition, patient reported outcome (PRO) instruments were developed and modified following additional qualitative research to better assess overall patient satisfaction comprising multiple body areas for treatment. This will be a global study to better inform CoolSculpting providers and patients worldwide about expected outcomes with the updated system and applicators, and to support a more patient-centric consultation and tailored treatment approach when multiple body areas are considered for treatment.

2.2. Background

CoolSculpting is a noninvasive, clinically proven fat-reduction treatment that selectively targets adipocytes using a patented cooling technology. The CoolSculpting mechanism of action is based on cryolipolysis, which works by cooling the subcutaneous tissue and preferentially targets adipocytes, leading to controlled elimination of adipocytes (Manstein 2008, Zelickson 2009). Adipose tissue appears more preferentially sensitive to cold injury than skin and other tissues (eg, skin, muscle, and nerve) and the crystallization of cytoplasmic lipids in adipocytes occurs at temperatures well above the freezing point of water (Epstein 1970, Beacham 1980, Manstein 2008).

In the United States, the CoolSculpting system first received FDA clearance in 2010 for noninvasive fat reduction in the flank followed by clearance for the abdomen in 2012 (Bernstein 2014). Further approvals were gained for 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.

The CoolSculpting System was first CE marked for fat layer reduction in 2009. The clearance was for general fat layer reduction, without a specified treatment area. Up to now, the CoolSculpting system has gained clearance/approval in more than 70 countries.

The latest iteration of the CoolSculpting System (CoolSculpting® Elite) initially received US FDA clearance on 21 Jan 2020 (510k clearance) and was first CE marked in Europe in November 2020.

Several enhancements to the predicate CoolSculpting device were made to develop CoolSculpting Elite and accommodate simultaneous applicator use. For the vacuum applicators, the applicator cup was updated to provide a single assembled unit incorporating the contour, thus eliminating the need for the gasket. Consequently, the geltrap on some applicators was repositioned to the top of the applicator, and the latches and contour interface were removed from the applicator housing. The applicator umbilical is lighter and more flexible. Changes were also made to the predicate's system control unit, vacuum, and chiller subsystems, hardware, and software to allow 1 or 2 treatments to be performed simultaneously. Simultaneous CoolSculpting Elite treatment consists of using Applicator A and Applicator B simultaneously. The applicator heating and cooling technology and method remain unchanged, utilizing the same thermoelectric coolers to achieve heating and cooling. The temperature feedback control mechanism remains the same and the device monitoring is through software monitoring.

The applicators are designed to treat most body areas, and there are 7 total body applicators that operate with the system (Curve 80, Curve 120, Curve 150, Curve 240, Flat 125, Flat 165, and Surface 150). The applicator consists of the applicator connector, the applicator umbilical, and the applicator head. All applicators except the Curve 80 and Surface 150 provide the ability to disconnect the handpiece from the umbilical.

While the CoolSculpting procedure is successful in reducing subcutaneous fat in various anatomical areas, patients often desire treatment in multiple body areas and typically more than one treatment session may be necessary to achieve desired results. Retrospective chart reviews indicate patients most commonly seek treatment for the abdomen and/or flanks and there is demand to treat other body areas beyond the midsection. In addition, physician feedback suggested that patients would prefer to have multiple CoolSculpting cycles performed at once in a single office visit to reduce the overall time of the procedures. [redacted]
The present study would expand the eligible body areas that can be treated to be reflective of real-world treatment consultations. In addition, capabilities of the device to allow for simultaneous use of applicators would allow for treatment of multiple body areas in the same or reduced treatment time.

A previous global (ex-US) study by Braun et al evaluated PROs via the CSQ, CGPQ, and CPIQ-Midsection (CPIQ-M) (Study CMO-MA-PLS-0602). These were created de novo to address treatment satisfaction with the abdomen only, flank only, or abdomen and flank together.

The study demonstrated high levels of patient satisfaction after CoolSculpting treatment for the abdomen and/or flanks with up to 24 cycles that could be delivered over two treatment sessions (the primary endpoint being 89.6% of participants rating their satisfaction with the fat reduction procedure as "Satisfied" or "Very Satisfied" on the CSQ Item 1). Patients also reported significant improvement in psychosocial impact after CoolSculpting treatment as measured by the CPIQ-M as well as measures derived from the CGPQ (which were exploratory endpoints). The findings demonstrated that patients benefited from tailored and optimized treatment plans to achieve their aesthetic goals in the abdomen and flank areas.

Given that the present study will also allow treatment of the inner thighs, outer thighs, submental area, and/or upper arms, the available PRO instruments required modification and qualitative patient research for the additional body areas. It was also important to further develop and refine a generalizable questionnaire considering that all of the above body areas could be included in the treatment plan. Hybrid concept elicitation/cognitive debriefing interviews were conducted with 12 participants to confirm the concepts and test the clarity and understanding of the following PRO measures: Cryolipolysis General Procedure Questionnaire – (CGPQ), Cryolipolysis Psychosocial Impact Questionnaire (CPIQ), CSQ-Overall, CSQ - Midsection, CSQ - Upper Arms, CSQ - Inner Thighs, CSQ - Outer Thighs, and CSQ - Fat under Chin.

In addition, this study will evaluate effectiveness by correct identification of baseline vs post-treatment images of the treated body area(s) by at least two out of three blinded, independent physician reviewers. This is consistent with prior CoolSculpting studies where independent photographic review was used for the correct identification of pre- vs final post-treatment visit images as a marker of visible improvement. Three-dimensional images will also be obtained at select study sites that have access to 3D imaging system to assess volumetric measurements.

A participant question will be administered (Participant Evaluation of Noticeable Improvement) to assess whether participant starts to observe noticeable improvement at 4 weeks post-treatment #1 with CoolSculpting Elite on the treated body areas. [redacted].

Although there are numerous clinical studies that have been conducted with the prior CoolSculpting system, there have been a limited number of patients who have been studied with the CoolSculpting Elite device and applicators globally with treatment plans facilitating simultaneous applicator use and multiple body areas. There is a need to evaluate effectiveness, safety, and patient-centric outcomes related to the CoolSculpting Elite procedure as well as to generate data with the updated applicators across body areas.

2.3. Benefits and Risks

2.3.1. Benefits

Non-invasive subcutaneous 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. Non-surgical fat reduction is one of the most frequent noninvasive cosmetic procedures and these procedures have become increasingly popular due to their convenience and accessibility. Patients who do not require significant fat reduction to achieve meaningful aesthetic results typically seek non-invasive fat reduction and body contouring procedures to avoid the pain, expense, downtime, and surgical risks associated

with invasive and minimally invasive procedures such as liposuction and laser-assisted liposuction. Over the last decade, the safety and effectiveness of cryolipolysis with CoolSculpting system for subcutaneous fat reduction has been well-established. In addition, patient satisfaction with cryolipolysis reported in the literature is consistently high. Advancements with the CoolSculpting Elite system in particular allow for dual applicator use that can shorten the overall time in clinic to complete treatment plan and provide for the opportunity to treat body areas simultaneously.

2.3.2. Risks

Although this study presents minimal risks to the participant, there is the potential for some risk when any cryolipolysis procedure is performed. The risks of using a CoolSculpting device can occur during and after the treatment and usually resolve within a few days. During the treatment, sensations of intense cold, numbness, tingling, cramping, pulling and mild pinching are expected due to the vacuum and cold temperatures to which the treatment area is subjected. Immediately after the treatment, it is common to see redness, firmness, bruising, swelling, as well as to have sensations of tingling, itchiness, numbness and pain on the treatment area. A sensation of fullness at the back of the throat may happen after a submental treatment.

Less commonly, the following side effects have been noted to occur after treatment, as outlined in the User's Manual: Paradoxical adipose hyperplasia that may require surgical intervention, late onset pain with typical onset several days after a treatment and resolution within several weeks, freeze burn that typically resolves without sequalae with proper care, hyperpigmentation and the additional events described in

Table 2-2.

The benefits of noninvasive fat reduction with CoolSculpting Elite treatment outweigh the risks.

Considering a pandemic or natural disaster, the benefit and risk to participants in this study has also been evaluated. Based on the limited information to date, no additional risk to study participants has been identified with the use of CoolSculpting Elite.

Anticipated Device Effects (Local effects of the treatment)

There 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 treatment with the CoolSculpting device 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
- Localized sensory changes (eg, numbness, tingling) at the treatment area spontaneously resolving without medical intervention within 12 weeks of the procedure

Anticipated device effects should not be reported as adverse events (AEs) unless the criteria below are met (Table 2-1).

When Anticipated Device Effects May Be Considered as Potential Adverse Events

If an anticipated device effect is considered severe, prolonged, results in treatment interruption or discontinuation and/or requires medical intervention as outlined below, then the event will need to be evaluated as a potential AE.

In addition to the anticipated device effects that meet the criteria of reporting as an AE, other reported AEs with CoolSculpting treatment are presented in Table 2-2.

Table 2-1 Guidance for Anticipated Device Effects

Anticipated Device Effect	Criteria for AE Reporting	Description for AE criteria
Bruising	Severe or prolonged	Severe: Bruising (purple discoloration); purpura (purple-colored spots or patches); or petechiae (pin point red dots) that causes disruption to the participant's daily activities as assessed by the study investigator. Prolonged: Bruising lasting longer than 1 month.
Erythema	Severe or prolonged	Severe: Erythema (redness) that causes disruption to the participant's daily activities as assessed by the study investigator. Prolonged: Erythema lasting longer than 2 weeks.
Swelling	Severe or prolonged	Severe: The appearance of swelling (edema) that causes disruption to the participant's daily activities as assessed by the study investigator. Prolonged: Swelling lasting more than 1 month.
Discomfort during procedure	Interruption/ discontinuation of treatment, or requiring medical intervention	Discomfort reported during the procedure that is intolerable to the participant and results in an interruption or discontinuation of the procedure.
Discomfort post procedure	Requiring medical intervention	Significant discomfort, pain, cramping, tenderness, soreness, or muscle spasm following the procedure which results in medical intervention (unplanned physician visit and/or prescription pain reliever).
Sensory Alteration	Severe or prolonged	Severe: Sensory changes (pain, burning, stinging, hypersensitivity) with a severity warranting medical intervention or causing disruption to the participant's daily activities as assessed by the study investigator Prolonged: Sensory changes (numbness, tingling, burning sensation) that are prolonged (ie, lasting longer than 12 weeks).

Table 2-2 Reported Adverse Events

Adverse Events	Description
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.
Severe pain	Patients may experience pain of varying severity, which more commonly can be described as mild to moderate, and in rare instances, can be severe.
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.
Vasovagal symptoms	The occurrence of symptoms of anxiety, light-headedness, dizziness, nausea, sweating, near-syncope, or syncope (fainting).
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 adipose hyperplasia	Visibly enlarged tissue volume within the treatment area which may become evident 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.
Treatment area demarcation	Treatment area demarcation: excessive fat removal in the treatment area causing unwanted indentation.
Other	Any other untoward medical event determined by the investigator to be an AE, regardless of the relationship to the device or treatment.

3. Objectives and Measures

Objectives	Measures
To evaluate participant satisfaction and effectiveness of the CoolSculpting Elite System using CoolSculpting Elite applicators for non-invasive subcutaneous fat reduction of the abdomen and flanks, upper arms, inner thighs, outer thighs and submental area	• Cryolipolysis Satisfaction Questionnaire (CSQ)-Midsection (abdomen and flanks) • CSQ-Overall (if additional body area(s) beyond abdomen and flanks are treated) • CSQ for individual additional body areas treated (upper arms, inner thighs, outer thighs, submental area) • Cryolipolysis General Procedure Questionnaire (CGPQ) • Cryolipolysis Psychosocial Impact Questionnaire (CPIQ) • Participant Evaluation of Noticeable Improvement • Photography and independent photography review (IPR) • 3D imaging of change in volume of fat
To evaluate safety of the CoolSculpting Elite System using CoolSculpting Elite applicators for non-invasive subcutaneous fat reduction of the abdomen and flanks, upper arms, inner thighs, outer thighs and submental area	• Adverse events (AEs) and adverse device effects (ADEs); serious adverse events (SAEs), serious adverse device effects (SADEs) • Unanticipated AEs or SAEs (previously unknown to the device) • Pain assessment

4. Study Design

4.1. Overall Design

This is a global, multicenter, multi-country, prospective, open-label, nonrandomized, interventional cohort, medical device post-marketing study evaluating the use of CoolSculpting Elite and CoolSculpting Elite applicators for noninvasive subcutaneous fat reduction of the abdomen, flanks, upper arms, inner thighs, outer thighs, and/or submental area in healthy volunteers. Participants will be enrolled at approximately 9 study sites.

Participants are eligible to receive up to two treatment sessions separated 8 weeks apart for the body areas eligible for treatment. Assessments will be completed 12 weeks after the final treatment session.

- If a participant receives only one treatment session for specific body area(s), the participant will return at Visit 8 for the 12-week post-treatment session 1 follow-up assessment and study exit.
- If a participant receives two treatment sessions for specific body area(s), the participant will return at Visit 9 for the 12-week post-treatment session 2 follow-up assessment and study exit.
- If a participant receives only one treatment session to a specific body area and two treatment sessions to another specific body area, the participant will return for both 12-week follow-up visits: Visit 8 for the 12-week post-treatment session 1 assessment of the body area that received only one treatment session and Visit 9 for the 12-week post treatment session 2 assessment of the body area receiving two treatment sessions; Visit 9 will also be the study exit visit for this participant.

Participant body areas selected for treatment during the study must be treated during the first treatment visit (Visit 2) and no new body areas may be treated at Visit 6. Participants planning to receive only one treatment session to a specific body area must have this treatment in Visit 2 during the first treatment session. Per investigator discretion, body areas identified for treatment may be treated simultaneously or sequentially. If sequential or simultaneous treatment is performed, there will be no difference in other treatment activities. Skin preparation, pain assessment, treatment site assessment, and post-massage, etc. will be identical in either case.

The study duration is up to approximately 20 weeks and consists of up to 7 scheduled study visits and 2 phone follow-ups per participant:

- Visit 1 (screening, Days -7 to 1)
- Visit 2 (treatment session #1, Day 1 + 3 days)

  Note: Treatment plan may be completed within a 7-day window from the day when the initial treatment is administered for this visit. The entire treatment session #1 plan for all the body areas selected for treatment must be completed within these 7 days.
- Visit 3 (1-week phone follow-up from last treatment day for participants who received treatment session #1 on any body area)

Note: If any of the following local effects of erythema, bruising, swelling, and/or sensory alteration are reported during Visit 3, additional phone follow-up (or in-person visit if aligned to planned study visit) will be scheduled in accordance with the time criteria outlined in Table 2-1 for potential AE categorization.

- Visit 4 (4-week follow-up after treatment session #1, Day 28 + 10 days)
- Visit 5 (8-week follow-up after treatment session #1, Day 56 + 14 days)
- Visit 6 (treatment session #2 [optional], Day 56 + 14 days, can be completed on the same day as Visit 5)

  Note: Only body area(s) that were treated at Visit 2 and that require a second treatment session are to be treated at Visit 6. The treatment plan for specific body area(s) may be completed within a 7-day window from when the initial treatment is administered for this visit. The entire treatment session #2 plan for the body area(s) selected for a second treatment must be completed within these 7 days.
- Visit 7 (1-week phone follow-up from last treatment day for participants who received treatment session #2 on any body area)

  Note: If any of the following local effects of erythema, bruising, swelling, and/or sensory alteration are reported during this Visit, additional phone follow-up (or in-person visit if aligned to planned study visit) will be scheduled in accordance with the time criteria outlined in Table 2-1 for potential AE categorization.
- Visit 8 (12-week follow-up/exit for participants with any body area that underwent only treatment session 1 at Visit 2, Day 84 + 14 days). If the participant receives only one treatment session to all body areas, this visit is also the study exit visit.

  Note: If the participant receives only one treatment session to a specific body area and two treatment sessions to another specific body area, the body area that received only one treatment session will be assessed at this visit. The participant will return at Visit 9 for assessment of body area that received two treatment sessions and study exit.
- Visit 9 (20-week follow-up/exit, corresponding to 12-week follow up for participants with any body area that underwent treatment session 2 at Visit 6, Day 140 + 14 days). If the participant receives two treatment sessions to any or all treated body areas, this visit is also the study exit visit.

Approximately 110 participants will be enrolled and approximately 96 participants are expected to complete the primary endpoint assessment based on an anticipated attrition rate of 12% or less.

During the course of the study, should it ever become necessary to remain isolated at home or to shelter-in-place per local, regional, or state pandemic-related orders, the sponsor will engage with study site staff in efforts to ensure the safety of participants, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage participant continuity of care. This may include alternative methods for assessments (eg, phone contacts or virtual site visits) in agreement with the sponsor. In all cases, these alternative measures must be allowed by local regulations and permitted by the Independent Review Board (IRB)/Independent Ethics

Committee (IEC). Investigators should notify the sponsor if any urgent safety measures are taken to protect the participants against any immediate hazard.

4.2. Scientific Rationale for Study Design

[redacted] There is a need to generate more information regarding the use of CoolSculpting when multiple body areas beyond midsection or torso are included for evaluation. In addition, there is no patient outcome reported data reflecting patient experience when multiple body areas are treated. In addition, this study will evaluate effectiveness by correct identification of baseline vs post-treatment images of the treated body area(s) by at least two out of three blinded, independent reviewers which is consistent with prior CoolSculpting studies for the specified treatment areas. The use of 3D imaging will also provide for evaluation of volumetric changes as a result of treatment. Therefore, there is a need to further evaluate the safety, effectiveness, and patient satisfaction with the CoolSculpting Elite System when cryolipolysis cycles are applied simultaneously or sequentially for noninvasive subcutaneous fat reduction for multiple body areas at an expanded number of clinical sites and across different patient populations.

4.3. Justification for Dose

For this device, the term “dose” refers to a single CoolSculpting Elite treatment cycle. A treatment cycle is defined as the attachment of a single applicator on body area delivering a timed segment of cooling. One or more treatment cycles will be delivered at the investigator’s discretion at each treatment session. Treatment cycles can be delivered simultaneously or sequentially at investigator discretion. Study site investigators will administer treatment cycles to participants according to the CoolSculpting Elite System User Manual. Up to 2 treatment sessions may be delivered for the abdomen and flanks, in addition to one or more of the optional body areas of treatment (upper arms, inner thighs, outer thighs, and submental area). Additional information regarding treatment cycles in provided in Section 6.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the final visit of the study which is 12 weeks post final treatment. [see the SoA in Table 1-1 or the study schema in Figure 1-1]).

The end of the study is defined as the date of the last visit of the last participant in the study.

If the participant is not able to present in person to the site for the Study Exit visit due to national or regional travel restrictions, site closure as a result of these restrictions, or a participant declines an in-clinic visit due to pandemic or natural disaster-related health concerns, a phone visit or alternate remote option is permitted.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant must be in good health as determined by medical history, physical examination, vital signs, and investigator's judgment, including no known active pandemic infection.
2. Participant (healthy volunteers) has read and signed the study written ICF.
3. Male or female participant 22 to 65 years of age inclusive at screening.
4. Participant has clearly visible and palpable fat in the abdomen and flanks, and participant may also be assessed for visible and palpable fat in one or more of the following body areas: left and right lower aspects of the upper arms, left and right inner thigh, left and right outer thigh, or submental area, which in the investigator's opinion is appropriate for and may benefit from treatment.
5. Participant agrees to receive treatment of the abdomen and flanks (collectively, the midsection) and has option to receive treatment to at least 1 additional body area listed in criterion 4.
6. Participant has not had weight change fluctuations exceeding 5% of body weight in the preceding month.
7. Participant has a BMI of ≥ 18.5 and < 30. BMI is defined as weight in kilograms divided by height in meters squared (kg/m^2).
8. Participant 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.
9. Participant agrees to have photographs taken of the treatment area(s) during the scheduled time periods.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Participant has a history of an invasive fat reduction procedure (eg, liposuction, surgery, lipolytic agents, etc) within or adjacent to the area being considered for treatment.
2. Participant has implants (eg, breast implants) in or immediately adjacent to the area of intended treatment.
3. Participant has a history of prior surgery or scar tissue related to the area being considered for treatment.
4. Participant has a known history of cryoglobulinemia, cold urticaria, cold agglutinin disease, or paroxysmal cold hemoglobinuria.

5. Participant has a 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, Raynaud's disease, or chilblains (pernio).
6. Participant with a clinically significant bleeding disorder, or concomitant use of blood thinners, or is taking any medication that, in the investigator's opinion, may significantly increase the participant's risk of bruising or bleeding. Participant on low dose aspirin for medical condition is excluded if the medical history suggests significant risk of bruising or bleeding per investigator's clinical judgement.
7. Participant has a history of carpal tunnel syndrome, compartment syndrome, or deep vein thrombosis in the upper or lower extremities (only applicable for participants receiving treatment to the upper arms or thighs).
8. Participant is currently taking or has taken diet pills or weight control supplements within the past 6 months.
9. Participant has any skin conditions, such as moderate to excessive skin laxity, open wound, or scars, and active infection, eczema, dermatitis or rashes in the location of the treatment sites that may interfere with the treatment or evaluation (stretch marks are not an exclusion).
10. Participant has an active implanted device such as a pacemaker, defibrillator, drug delivery system, or any other metal-containing implant, within or adjacent to the area being considered for treatment.
11. Participant (WOCBP) is pregnant or intending to become pregnant in the next 3 to 6 months and does not agree to use reliable contraception during the study.
12. Participant is lactating or has been lactating in the past 6 months.
13. Participant is unable or unwilling to comply with the study requirements.
14. Participant 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.
15. Participant has any other condition or laboratory value that would, in the professional opinion of the investigator, potentially affect the participant's response or the integrity of the data or would pose an unacceptable risk to the participant.
16. Participant has had a non-invasive fat reduction and/or body contouring procedure in the area(s) of intended treatment within the past 12 months.
17. Participant 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.
18. Participant with known sensitivity or allergy to fructose, glycerin, isopropyl alcohol, or propylene glycol.
19. Participant has impaired peripheral circulation in the area to be treated.
20. Participant has neuropathic disorders such as post-herpetic neuralgia or diabetic neuropathy.

21. Participant has impaired skin sensation in or immediately adjacent to the treatment area(s).
22. Participant has a history of hernia in or immediately adjacent to the treatment area(s).
23. Participant diagnosed with a systemic fibrosing disease or fibrosis in the area intended or adjacent to the area to be treated.

5.3. Lifestyle Considerations

Lifestyle considerations are not applicable to this study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AE.

6. Study Intervention

Study intervention is defined as the medical device (CoolSculpting Elite System and CoolSculpting Elite applicators) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention Administered (CoolSculpting Elite System)

Participants will undergo a CoolSculpting Elite treatment in an outpatient clinical setting. A treatment is comprised of timed segments of cooling (treatment cycle) followed by 2 minutes of manual massage. Treatments will be administered according to the CoolSculpting Elite user manual that has been prepared for specific countries and provided to the study sites. All device deficiencies (including malfunction and use error) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.8) and appropriately managed by the sponsor.

6.1.1. Identity of the CoolSculpting Elite System

The CoolSculpting Elite System is a portable thermoelectric cooling and heating device that applies controlled cooling or heating to a treatment site on the participant's skin. The system has two umbilicals attaching the applicators to the control unit to allow dual applicator use at the same time. The system is comprised of a control unit, applicators, and supplies such as cards, gelpads, pretreatment skin wipes, liners, foam borders, securement grip, support arm and comfort straps. The applicators, gelpads, pretreatment skin wipes, liners, foam borders, and comfort straps are parts applied to patient. During a treatment, the operator applies a gelpad and applicator to the patient's skin. For a treatment where two or more applicators are used simultaneously, additional applicators are applied with another gelpad. The applicator(s) draw tissue into the applicator cup(s) and hold(s) the tissue against the cooling surfaces of the applicator(s). The operator then starts the treatment. The Surface S150 applicator does not draw in tissue and does not have a cup. The treatment card (can be referred to as "Standard" card or "SOLO" card depending on country) provides treatments and profiles for use with the system.

During the cooling treatment, sensors in the cooling surfaces of the applicator(s) monitor the skin surface and provide feedback [redacted]. The gelpad(s) protect the skin by providing thermal coupling at the interface between the cooling surfaces of the applicator(s) and the skin.

The CoolSculpting Elite System operates applicators at temperatures below 0°C. 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.

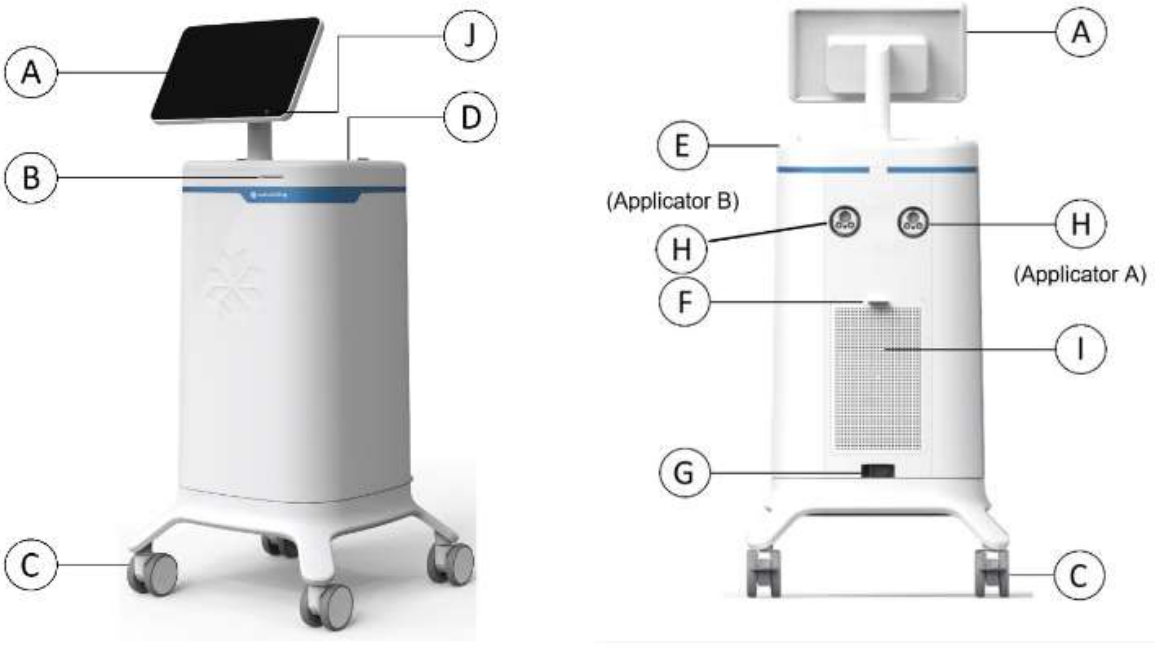
The Freeze Detect system is comprised of several features, including thermal sensors and proprietary algorithmic software. Freeze Detect is an integral part of the CoolSculpting System and is automatically employed when a treatment is initiated. When the Freeze Detect system detects a possible freeze 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 hyper- or hypopigmentation.

6.1.2. Control Unit

The control unit is shown in Figure 6-1. For additional detail, please see the CoolSculpting Elite System user manual.

Figure 6-1 CoolSculpting Elite Control Unit



- (A) Touchscreen display: The touchscreen displays system controls, information about the status of the system, information about the treatment, and messages for the operator. You can rotate or tilt the display to accommodate better access.
- (B) Card Slot: The card slot accepts treatment cards. You must insert an appropriate SOLO treatment card with active treatments in order to begin the procedure.
- (C) Casters and locks: The control unit has four casters that swivel. Each caster has a lock. Always engage all four caster locks when the unit is stationary. Disengage the caster locks to move the unit.
- (D) Bucket: The bucket is a storage area for applicators and/or consumables. You can remove the bucket from the control unit for cleaning.
- (E) Top cap lip: When the applicator is resting on top of the control unit, the top cap lip helps keep the applicator in place.
- (F) Access panel: The access panel covers vents, a USB port, and the chiller tank cap.

- (G) Power receptacle and power switch: The power receptacle houses the plug for the power cord. The power switch controls the power to the control unit and system components. Contact customer service if the power entry mode appears to be broken.
- (H) Connector ports for umbilical cords for applicators A and B: The control unit has two connector ports where two umbilical cords attach to perform a simultaneous treatment. Simultaneous treatment is an option, but not necessary.
- (I) 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.
- (J) Soft power button: The display includes a soft power button at the lower right corner, which is used to power on the system, after turning the power switch on the rear of the system to the "On" position. The soft power button may also be used to power off the system.

6.1.3. Applicators

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 the sponsor.

Always use gelpads with the applicator. The applicators are designed to treat most body areas. Investigators should consider all physical aspects of the area to be treated and use the applicator that will fit best for each participant and body area being treated.

The CoolSculpting Elite applicators available in this study depend on country clearances and can include Curve 240, Curve 150, Curve 120, Flat 165, Flat 125, Surface 150, and Curve 80.

For additional details regarding applicators, please see the CoolSculpting Elite user manual.

6.2. Additional Study Intervention Supplies

The following supplies will be provided to support use of the CoolSculpting Elite System:

- Card: Provides treatment cycles and profiles for use with the system
  - Profiles define the number of timed segments of cooling
  - Each treatment cycle provides a single treatment
- Coolant: The control unit requires an adequate supply of coolant (from the manufacturer). When the coolant level is low, the system displays a recoverable exception message.
- Gelpad: Provides thermal contact between the applicator and the participant's skin and mitigates minor variances in device-to-skin contact (note: this is a single-use item; use a new gelpad for each treatment).
- Gel trap: Fits into the slot of the applicator and prevents the ingress of gel into the vacuum system (note: this is a single-use item, use a new gel trap for each treatment).
- Pretreatment skin wipe: Use the pretreatment skin wipe to prepare the treatment site before applying a gelpad (note: this is a single-use item; use a new pretreatment skin wipe for each treatment).

- Securement system: minimizes movement of the applicator during treatment.
- Liner (applies to Surface 150 applicator only): provides an interface between the gelpad and applicator.
- Foam border (applies to Surface 150 applicator only): minimizes movement of the surface applicator during treatment.
- Securement grip (applies to Surface 150 applicator only): minimizes movement of the surface applicator during treatment.
- Support arm (applies to Curve 80 applicator only): intended for use in supporting the C80 applicator head during treatment.

For additional details, please see the CoolSculpting Elite user manual.

6.3. Randomization and Blinding

Blinding is not applicable to this open-label, nonrandomized 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.

At screening, after the participant has signed the 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.

6.4. Study Intervention Compliance

When participants are treated at the study site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each treatment session administered in the clinic will be recorded in the source documents and the eCRF.

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 or protocol deviation, as defined below.

Protocol Violation

A violation is any non-adherence to the protocol that may result in significant additional risk to the participant (eg, enrollment of a participant who does not meet the study criteria). A protocol violation can also be an event of non-adherence to GCPs that may impact participant safety (eg, failure to obtain proper consent before performing study procedures). Violations should be reported to the study sponsor and the 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 participant (eg, participant missed a visit). Protocol deviations are not required to be reported to the IRB; however, they must be recorded on the study eCRFs and may be reported and reviewed in conjunction with the progress report as part of the annual review process.

6.5. Concomitant Therapy

All concomitant medications including vaccinations and procedures will be recorded on the eCRFs. Concomitant medications that are part of routine care are allowed and can be used during the study.

6.5.1. Prohibited Therapy

Diet pills or weight control supplements are not permitted (see Section 5.2, exclusion criterion # 8). Concomitant use of blood thinners, or any medication or dietary supplement that increases the risk of bruising such as fish oil, garlic, ginkgo, and vitamin E are not permitted. Participant on low dose aspirin for medical condition is excluded if the medical history suggests significant risk of bruising or bleeding per investigator's clinical judgement. Concomitant use of surgical or nonsurgical fat reduction or body contouring procedures (eg, radiofrequency lipolysis, low-level laser therapy, high-intensity focused ultrasound, electromagnetic muscle stimulation) or injectable lipolytic agents during the course of the study are not permitted (see Section 5.2, exclusion criterion #1, 16).

Additionally, at the discretion of the investigator, any topical creams or other medications that may impact the safety or effectiveness of the treatment are not permitted.

6.6. Dose Modification

For this device, the term "dose" refers to a CoolSculpting Elite treatment cycle. One or more treatment cycles will be delivered at the investigator's discretion at each treatment session. Treatment cycles can be delivered simultaneously or sequentially at investigator discretion during a treatment session. Study site investigators will administer up to 2 treatment sessions to the treatment areas in accordance with the CoolSculpting Elite System User Manual.

All participants entered into the study will receive a CoolSculpting treatment session (Visit 2) for the body areas selected for treatment. A participant may receive an additional treatment session at Visit 6 for body areas that were treated at Visit 2 as determined by the investigator.

Guidance for the recommended/required range of treatment sessions and treatment cycles by body area, and overall, is presented in Table 6-1.

Table 6-1 Guidance for Number of Treatment Sessions and Treatment Cycles Per Body Area

Body Area	Minimum Number of Treatment Sessions	Maximum Number of Treatment Sessions	Maximum Number of Treatment Cycles Per Treatment Session	Maximum Total Number of Treatment Cycles
Abdomen and flanks (Midsection)	1	2	8	16
Upper Arms (inclusive of both left and right arm)	0	2	4	8
Inner Thighs (inclusive of both left and right inner thigh)	0	2	4	8
Outer Thighs (inclusive of both left and right outer thigh)	0	2	4	8
Submental	0	2	2	4

6.7. Intervention after the End of the Study

There is no intervention planned after the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and receives study intervention ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF.

Reasons for discontinuation from the study intervention and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Lost to follow-up	Disease relapse
Other	Progressive disease
Physician decision	Technical problems
Pregnancy	
Protocol deviation	
Screen failure	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by participant	

7.1. Discontinuation of Study Intervention

During the treatment, study intervention may be discontinued due to significant discomfort, wellness issues, psychological issues, or the participant's refusal to continue the treatment.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. The following data should be collected at the time of study exit and follow-up and for any further evaluations that need to be completed:
  - Date of discontinuation from the study
  - Reason for discontinuation/withdrawal from the study
  - Date of study completion, if applicable

- If discontinued due to AE or device deficiency, complete the relevant eCRF and SAE/Device forms
- If discontinued due to pregnancy, complete the Pregnancy form
- Clinical assessment of treated areas for potential AEs.
- Participants withdrawing from the study will be encouraged to complete the same final evaluations as participants completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for participants who completed the study.

- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- During the course of the study, it may be necessary to employ mitigation strategies to enable the investigator to ensure participant safety and continuity of care. Acceptable mitigation strategies are identified and included in Section 8.

The investigator should contact the sponsor before discontinuing a participant from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 phone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is discussed in Section 10.1.8.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Table 1-1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- If the participant is not able to present in person to the site for the Study Exit visit due to national or regional travel restrictions, site closure as a result of these restrictions, or a participant declines an in-clinic visit due to pandemic or natural disaster-related health concerns, a phone visit or alternate remote option is permitted.

8.1. Effectiveness Assessments

Effectiveness assessments will include the CSQ (6 versions), CGPQ, CPIQ, Participant Evaluation of Noticeable Improvement, independent photo review of 2D participant before and after photos, and 3D imaging to assess volumetric change of treated area, where available. [redacted]

Planned time points for all effectiveness assessments are provided in the SoA (Table 1-1).

If travel restrictions or other changes in local regulations in the case of a pandemic or natural disaster prevent the participant from in-person visits, some study assessments may be conducted remotely or via phone or video conference.

8.1.1. Patient-reported Outcomes

Participant satisfaction, experience with procedure, and psychosocial impact data will be collected via paper questionnaires. These questionnaires have been developed and modified following additional qualitative research based on questions used in previous CoolSculpting studies. The questionnaires include the CSQ-Midsection (Section 10.6), CSQ-Overall (Section 10.7), CSQ-Upper Arms (Section 10.10), CSQ-Inner Thighs (Section 10.9), CSQ-Outer Thighs (Section 10.8), CSQ-Fat under chin (Section 10.11), CGPQ (Section 10.12), and CPIQ (Section 10.13).

The CSQ-Midsection is a 2-item PRO instrument that measures participant satisfaction with results of CoolSculpting treatment and improvement in fit of clothing. CSQ-Overall and the CSQ specific for body area are 1-item PRO instruments that measure participant satisfaction with results of treatment when considering all body areas treated and individual body area, respectively. The CGPQ is a 5-item PRO instrument that assesses participant experience with the CoolSculpting treatment procedure. The questionnaire assesses participant comfort with the

treatment, likelihood of having another fat reduction procedure on a different part of the body, likelihood of recommending the procedure to a friend, and satisfaction with length of time to complete the procedure and achieve visible results. The CPIQ is a 5-item PRO instrument that assesses the psychosocial impact of CoolSculpting treatment, including self-confidence, feeling unhappy, feeling anxious, feeling bothered, and avoiding certain places or situations.

An additional participant question (Participant Evaluation of Noticeable Improvement) will be administered 4 weeks after the first treatment session to assess whether participant starts to observe noticeable improvement with CoolSculpting Elite on the treated body areas at this earlier timepoint (Section 10.14).

8.1.2. Photography

A series of baseline and follow-up 2D photographs of the treatment areas will be taken using standardized set-up, lighting, and camera settings to ensure consistency. Where participant identifiable markings are seen within the treatment area, the images containing these markings will be masked for the purpose of publications but kept as part of the study record in the trial master file. The photographs may be cropped or re-sized for comparison purposes but otherwise will not be re-touched or altered in any way. Image files will be stored electronically by the sponsor in addition to Canfield Scientific (Parsippany, New Jersey, USA) and indexed by participant identifier. Participant photographs will be filed at the clinical site.

Photos will be reviewed by a blinded independent panel of three 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. Post-treatment images will correspond to 4-weeks post treatment session 1 and 12-weeks post final treatment session for the respective treated body areas. 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.

Select study sites that have access to Canfield 3D imaging system will also capture 3D images for purposes of assessment of volumetric changes. The 3D imaging system will be used to obtain a 360 degree image of the body to allow quantification of the treated areas, specifically, volumetric changes from baseline.

For additional detail regarding participant photography, please see documentation created by Canfield Scientific (imaging vendor).

8.1.3. Other Assessments

[redacted]

If travel restrictions or other changes in local regulations in case of a pandemic or natural disaster prevent the participant from in-person visits, some study assessments may be conducted remotely or via phone or video conference.

8.2. Safety Assessments

Safety assessments will include pain assessments, AEs, SAEs, ADEs, SADEs, and unanticipated AEs or ADEs.

Planned time points for all safety assessments are provided in the SoA (Table 1-1). If travel restrictions or other changes in local regulations in light of a pandemic or natural disaster prevent the participant from in-person visits, participant visits may be conducted via phone or video conference or at an alternative location. The investigator should contact the sponsor in advance, if possible, to discuss how vital signs should be handled.

8.2.1. Pain Assessment Score

At Visits 2 and 6 (treatment session 1 and 2 visits), participant pain will be assessed 10 minutes after starting the cooling treatment using a standard scale of 0 to10, 0 being no pain and 10 being the worst pain imaginable during the treatment cycle. If the pain score worsens during the treatment, this will also be recorded. If discomfort is intolerable, the treatment will be discontinued until the participant is comfortable and treatment, at the discretion of the investigator, can be resumed. Discomfort that results in either a temporary or permanent cessation of the treatment is to be documented as an AE (for additional detail, see Table 2-1 [guidance for anticipated device effects] and Section 8.3 [AEs]).

At Visits 3, 4, 5, 6, 7, and 8, 9 (all other study visits), participant pain will be assessed using a standard scale of 0 to 10, 0 being no pain and 10 being the worst pain imaginable.

8.2.2. Treatment Site Assessment

Immediately post treatment and prior to massage, the treatment site(s) will be examined for any epidermal, dermal, or subcutaneous findings (eg, blanching, erythema, bruising, swelling); alterations in sensation (eg, numbness, tingling). For additional detail, please see Table 2-1 (guidance for anticipated device effects) and Section 8.3 (AEs).

8.2.3. Other Laboratory Assessments

Screening for pregnancy will be performed (urine β-HCG) for WOCBP and a negative result must be achieved before initiating treatment.

8.2.4. Suicidal Ideation and Behavior Risk Monitoring

Suicidal ideation and behavior risk monitoring are not applicable to this study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.5. The definitions of device-related safety events (ADEs and SADEs) can be found in Section 10.5. Device deficiencies are covered in Section 8.3.8.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, ADE, SAE, SADE, and any other study-specific terms as relevant and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be recorded in the AE sections of the eCRF throughout the study periodTable 1-1 as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded in the CRF and reported to the sponsor or designee using a SAE form immediately; and under no circumstance should this exceed 24 hours, as indicated in Section 10.5. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek all AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Pandemic infections should be captured as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions per the protocol.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of all AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.5.

Care will be taken not to introduce bias when detecting all AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of All AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow up with each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.5.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with other documents and will notify the IRB/IEC, if appropriate, according to local requirements.

8.3.5. Pregnancy

- Female participants will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy using the Pregnancy Surveillance Form and should follow the procedures outlined in Section 10.4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs and should follow the SAE reporting procedure outlined in Section 10.4.

8.3.6. Protocol-specific AEs

Not applicable.

8.3.7. Adverse Events of Special Interest

Not applicable.

8.3.8. Medical Device Deficiencies

Medical devices (CoolSculpting Elite System and CoolSculpting Elite applicators) are being provided for use in this study as the study intervention. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.5. Examples of commonly reported device deficiencies are: warnings of thermal events/freeze detect, applicator errors, system shutting down spontaneously during the treatment, lost cycle error, burning smell or smoke from the device, and multiple (>1) pop offs with the same applicator. Single applicator pop off events should not be reported as a device deficiency.

NOTE: Deficiencies associated with the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Section 10.5 of the protocol.

Additional guidance for thermal events and pop offs is provided in Table 8-1.

Table 8-1 Investigator guidance for thermal events and pop offs

Event	Guidance
Thermal event	Report all thermal events as device deficiencies. If a thermal event is associated with an AE (eg, burn), AE should also be reported.
Pop off	Multiple pop offs with the same applicator during the treatment session, irrespective of body area, should be reported as a device complaint. Single pop off during a treatment session should not be reported as a device complaint.

8.3.8.1. Time Period for Detecting Medical Device Deficiencies

Medical device events or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

The method of documenting a medical device deficiency is provided in Section 10.5.

8.3.8.2. Follow-up of Medical Device Deficiencies

- AEs resulting from medical device deficiencies will be followed up.
- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.8.3. Prompt Reporting of Device Deficiencies to Sponsor

- Device deficiencies will be recorded on the eCRF and reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- If a device deficiency is associated with an SAE, the Medical Device Deficiency section on the SAE Form will be sent to the sponsor by email in addition to recording in the eCRF. If email is unavailable, then fax should be utilized.
- Device deficiencies not associated with AEs will be recorded on the eCRF. A non-medical complaint form will be emailed to the sponsor as specified in Section 10.5.
- The sponsor will be the contact for the receipt of device deficiency reports.

8.3.8.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4. Treatment of Overdose

Treatment of overdose is not applicable to this study.

8.5. Pharmacokinetics

Pharmacokinetics is not applicable to this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not applicable to this study.

8.7. Genetics

Genetics are not applicable to this study.

8.8. Biomarkers

Biomarkers are not applicable to this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not applicable to this study.

8.10. Health Economics

Health economics are not applicable to this study.

9. Statistical Considerations

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses.

9.1. Statistical Hypotheses

No statistical hypotheses are planned to be tested.

9.2. Sample Size Determination

The sample size will be based on providing reasonable precision for the estimate of the overall satisfaction rate. The estimate is based on overall satisfaction rates of the various body areas treated with CoolSculpting.

Previous studies conducted on participants undergoing flank or abdominal fat reduction using the CoolSculpting device reported moderately high overall satisfaction rate. [redacted] A sample size of 96 participants would provide a two-sided 95% confidence interval (CI) with a width equal to 0.2 when the overall satisfaction rate is 63.9%. Exact (Clopper-Pearson) method from the commercial software PASS 2008 was used for the sample size calculation. Allowing for a 12% attrition rate during the study period, approximately 110 participants will be needed for recruitment into the study.

If local guidelines are in effect to prevent and mitigate the effects of a pandemic or natural disaster, it is possible that some participants may not be able to complete all site visits as indicated per protocol. To preserve the sample size calculation, additional participants may be enrolled if more than 12% of the participants fail to complete the CSQ-Midsection Item 1 at 12 weeks after the final treatment.

9.3. Populations for Analyses

The following populations are defined for statistical analyses:

Population	Description
Enrolled	The enrolled population will consist of all participants who sign the informed consent.
Safety	The safety population will consist of all enrolled participants who receive a cryolipolysis treatment cycle (started or completed).
Evaluable	• The evaluable population for the primary endpoint will consist of all treated participants who completed the cryolipolysis treatment plan to the midsection and who completed the CSQ-Midsection Item 1 at 12 weeks after the final treatment measured at Visit 8 (Week 12) for participants who receive 1 treatment session and at Visit 9 (Week 20) for participants who receive 2 treatment sessions. • The evaluable population for other effectiveness endpoints will consist of all treated participants who completed the cryolipolysis treatment plan for any other body areas (whether midsection treatment completed or not).

9.4. Statistical Analyses

The SAP will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary, secondary, and exploratory endpoints.

9.4.1. General Considerations

In general, disposition data will be summarized for all enrolled participants, and participant baseline and characteristics data, and concomitant therapy data will be summarized descriptively for the safety population. The categorical variables will be presented with number and proportion while the continuous variables will be presented with mean, standard deviation, median, minimum, and maximum.

The effectiveness analyses will be based on the evaluable population and the safety analyses will be based on the safety population. Baseline for effectiveness is defined as the last non-missing effectiveness assessment before the first treatment session. All CIs will be 2-sided 95% CIs, unless stated otherwise.

9.4.1.1. Main Analytical Approach

Participants who have reported “satisfied” and “very satisfied” will be categorized as ‘Satisfied.’ The counts and percentages will be summarized and the 95% CI on the percentage will be provided.

9.4.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is the proportion of participants with "satisfied" or "very satisfied" on the item 1 for the CSQ-Midsection, measured at Week 12 (Visit 8) for participants who receive 1 treatment session, or at Week 20 (Visit 9) for participants who receive 2 treatment sessions.

9.4.3. Secondary Effectiveness Endpoints

- The proportion of participants who received treatment to abdomen and flank and one or more additional body areas for treatment with "satisfied" or "very satisfied" on CSQ-Overall Item 1 measured at Week 12 (Visit 8,12-week follow-up for participants who receive only 1 treatment session to all treated body areas) or at Week 20 (Visit 9, 12-week follow-up for participants who receive 2 treatment sessions to any or all treated body areas).
- The proportion of participants with "satisfied" or "very satisfied" on individual treated body area (upper arms, inner thighs, outer thighs, fat under chin) CSQ Item 1 measured at Week 12 (Visit 8, 12-week follow-up for participants who receive only 1 treatment session) or at Week 20 (Visit 9,12-week follow-up for participants who receive 2 treatment sessions) for the respective treated body areas.
- Correct identification of baseline vs 12-week post-final treatment images of the treated body area(s) by at least two out of three blinded, independent reviewers for the following body areas:
    - Midsection
    - Upper arms
    - Inner thighs
    - Outer thighs
    - Submental area

Success will be defined as at least 70% correct identification of the pre-treatment images.

9.4.4. Exploratory Effectiveness Endpoints

The analyses on the exploratory endpoints will include:

- Psychosocial impact for non-invasive fat reduction in CoolSculpting participants using the CPIQ
- Experience with fat reduction procedure using the CGPQ
- Improvement in fit of clothing using CSQ-Midsection Item #2
- Proportion of participants reporting noticeable improvement at 4-weeks post treatment session 1
- 3D volumetric change from baseline

- Correct identification of baseline vs 4-week post treatment session 1 images of the treated body area(s) by at least two out of three blinded, independent reviewers for the following body areas:
  - Midsection
  - Upper arms
  - Inner thighs
  - Outer thighs
  - Submental area

Success will be defined as at least 70% correct identification of the pre-treatment images.

Exploratory effectiveness endpoints will be summarized similar to the primary effectiveness endpoint with 95% CIs.

9.4.5. Safety Analyses

The numbers and proportions of participants with AEs, SAEs, ADEs, SADEs, and unanticipated AEs or ADEs will be summarized. Additional details pertaining to safety analyses will be provided in the SAP.

9.4.5.1. Adverse Events

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of study intervention.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

The number and percentage of participants with TEAEs will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants with TEAEs will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Summary tables will be provided for participants with TESAEs, TESADEs, TEADEs, and participants with TEAEs leading to discontinuation if these occurred in 5 or more participants. Listings of all AEs, SAEs, SADEs, ADEs, device deficiencies, and AEs leading to discontinuation by participant will be presented.

9.4.5.2. Pain Assessment

Pain assessment 10 minutes after starting the cryolipolysis treatment using a standard scale of 0 (no pain) to10 (10 being the worst pain imaginable) will be summarized descriptively (number and percentage of participants who experienced pain level).

9.4.5.3. Medical Device Deficiencies

The numbers and proportions of participants with anticipated device effects will be summarized descriptively.

9.4.6. Subgroup Analyses

Subgroup analyses will be defined and documented in the SAP.

9.5. Interim Analyses

No interim analyses are planned for this study.

9.6. Data Monitoring Committee

Not applicable.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the CIOMS International Ethical Guidelines
  - Applicable ICH/ISO GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- During the course of the study, should it ever become necessary to remain home or to shelter-in-place per local, regional, or state orders, the sponsor will engage with study site staff in efforts to ensure the safety of participants, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage participant continuity of care. This may include alternative methods for assessments (eg, phone contacts or virtual site visits) in agreement with the sponsor. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify the sponsor if any urgent safety measures are taken to protect the participants against any immediate hazard.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- In the event of a pandemic or natural disaster, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. Any verbal consent must be dated and documented in the source document.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; any identifiable participant information will only be transferred in accordance with the signed Informed Consent provisions.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local privacy and data protection laws. The level of disclosure must also be explained to the participant who will be required to give consent for their personal data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Management of privacy incidents relating to clinical trial participant personal data, as well as handling of data participant rights requests (if applicable), should be handled in accordance with the agreed-upon Clinical Trial Agreement (CTA) provisions.

10.1.5. Dissemination of Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the United States National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the contracts.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In the event of a pandemic or natural disaster, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, GCP: Consolidated Guidance and records must be attributable, legible, contemporaneous, original, and accurate.

10.1.8. Study and Site Start and Closure

For the purpose of clinical trial registries, the study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is first patient first visit and is considered the first act of recruitment and will be the study start date.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up. If a premature termination or suspension occurs, the sponsor shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of participants enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled participants, if applicable.

10.1.9. Publication Policy

- The sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor personnel. Authorship will be established prior to the writing of the manuscript.
- The sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements including those that may be due to a pandemic or natural disaster.

10.2. Appendix 2: Abbreviations

Abbreviation	Definition
ADE	adverse device effect
AE	adverse event
AESI	Adverse event of special interest
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CE	Conformité Européenne
CGPQ	Cryolipolysis General Procedure Questionnaire
CI	confidence interval
CIOMS	Declaration of Helsinki and Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CPIQ	Cryolipolysis Psychosocial Impact Questionnaire
CRF	case report form
eCRF	electronic case report form
CSQ	Cryolipolysis Satisfaction Questionnaire
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
IPR	independent photography review
IRB	institutional review board
ISO	International Organization for Standardization
IUD	Intrauterine device
IUS	Intrauterine system
NCI	National Cancer Institute
PRO	patient-reported outcome
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
TEADE	treatment-emergent adverse device event
TEAE	treatment-emergent adverse event
TESADE	treatment-emergent serious adverse device event
TESAE	treatment-emergent serious adverse event
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect
WOCBP	woman of childbearing potential

10.3. Appendix 3: Standard Discontinuation Criteria

This table provides participant discontinuation criteria for this protocol. CDISC terminology is used, and thus *subject* or *patient* is used instead of *participant* (as used elsewhere in this protocol). These terms are interchangeable.

CDISC Submission Value	CDISC Definition
AE	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also SAE, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion, or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth (NCI).
Progressive disease	A disease process that is increasing in extent or severity (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)

CDISC Submission Value	CDISC Definition
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by parent/guardian	An indication that a study participant has been removed from the study by the parent or legal guardian
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective or acceptable method of contraception consistently and correctly as described in Table 10-1.

Table 10-1 Highly Effective and Acceptable Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) • Bilateral tubal occlusion (eg, Essure®, bilateral tubal ligation) • Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Acceptable Methods *Acceptable birth control methods that result in a failure of more than 1% per year include:*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide • Nonhormonal intrauterine device A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

10.4.3. Pregnancy Testing

Pregnancy testing will be performed (urine β-HCG) for WOCBP and a negative result must be achieved before initiating treatment.

Collection of Pregnancy Information

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be SAEs and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be discontinued from the study.

10.5. Appendix 5: AEs, ADEs, SAEs, SADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study.

10.5.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subject, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. Note 1 to entry: This definition includes events related to the investigational medical device or the comparator. Note 2 to entry: This definition includes events related to the procedures involved. Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events 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 or from intentional misuse of the investigational medical device. This includes "*comparator*" if the comparator is a medical device. • An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study intervention or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it. There are no AESIs identified for this study intervention(s).

10.5.2. Definition of SAE, SADE, and USADE/UADE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury. The term 'life-threatening' in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe 2. A permanent impairment of a body structure or a body function 3. Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function 5. Chronic disease (Medical Device Regulation 2017/745)
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect
SADE definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
USADE/UADE definition
• A USADE (also identified as UADE in US Regulations 21 CFR 813.3), defined as a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.5.3. Definition of Device Deficiency

Device Deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

10.5.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF. • In addition to recording on the eCRF, SAEs should be reported to the sponsor on the SAE form. If an SAE is associated with device deficiency, the relevant device information should be completed on the SAE form. • Device complaints that are not associated with AEs should be recorded on the eCRF form. Additionally, "Non-Medical Complaint Form" should be completed and emailed to "IR-GPDC-non-medicalcomplaints@Allergan.com" • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE/SAE/device deficiency eCRF page. • There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. • For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.   • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

- The following data should be documented for each event in the appropriate eCRF fields: 1. Description of the symptom event. 2. Classification of 'serious' or 'not serious.' 3. Severity. 4. Date of first occurrence and date of resolution (if applicable). 5. Action taken. 6. Causal relationship. 7. Outcome of event.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE reported during the study and assign it to one of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities or daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, *not* when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the device user manual in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of Device Relationship

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 has an 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 where 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 AE/SAE/device deficiency
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology. • Investigators should follow up with participants 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 eCRF. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information. • AEs and device deficiencies (complaints) will be recorded in the eCRF. • SAEs/SADEs and device deficiencies associated with AEs will be recorded in the eCRF as well as reported to the sponsor on the SAE form or forms within 24 hours of awareness. • Device deficiency not associated with AEs will be reported to the sponsor using non-medical device deficiency form.

10.5.5. Reporting of SAEs

SAE Reporting to Sponsor or Designee Within 24 Hours
• Contacts for SAE reporting can be found on the protocol title page. • Email is the preferred method to transmit SAE information. • Facsimile transmission of the SAE information is also acceptable. In addition to recording the SAEs in the eCRF, an SAE form should be completed and sent to the sponsor within 24 hours of awareness to the email address provided on the table below.

10.5.6. Reporting of SADEs

SADE Reporting to Sponsor or Designee
NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for SAE reporting can be found on the protocol title page.

Email/Fax for SAE /SADE Form Reporting:

For US and all other countries outside the EU:	Fax: +1-877-605-4524 or +1-714-796-9567 Email: LC-Medical_Safety@Allergan.com
For EU:	Fax: +1-714-954-6055 Email: DL-LC-Global_Safety_Reporting@Allergan.com
Medical Device Complaint Reporting	Email: IR-GPDC-non-medicalcomplaints@Allergan.com

Note 1: Device complaints associated with SAEs should be reported in the device section of the SAE form.
Note 2: All AEs, SAEs, and Device Complaints should be recorded on the eCRF.

10.6. [redacted]

[redacted]

10.7. [redacted]

[redacted]

[redacted]

10.8. [redacted]

[redacted]

[redacted]

10.9. [redacted]

[redacted]

[redacted]

10.10. [redacted]

[redacted]

[redacted]

10.11. [redacted]

[redacted]

10.12. [redacted]

[redacted]

[redacted]

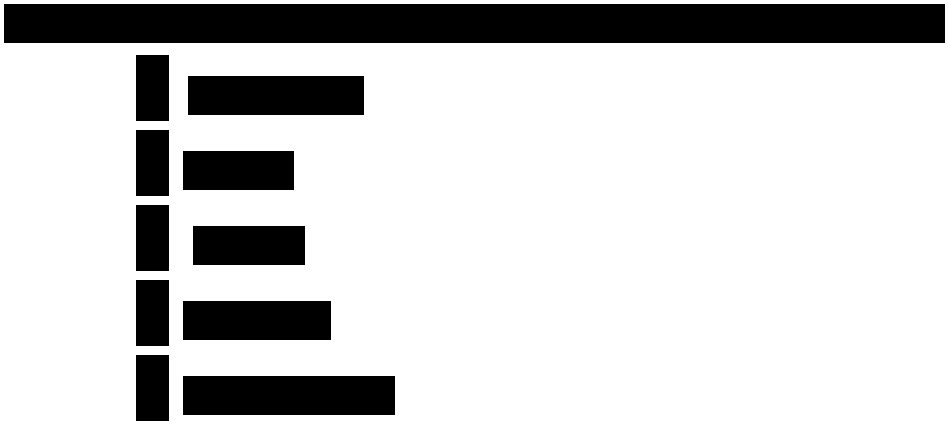
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]



10.13. [redacted]

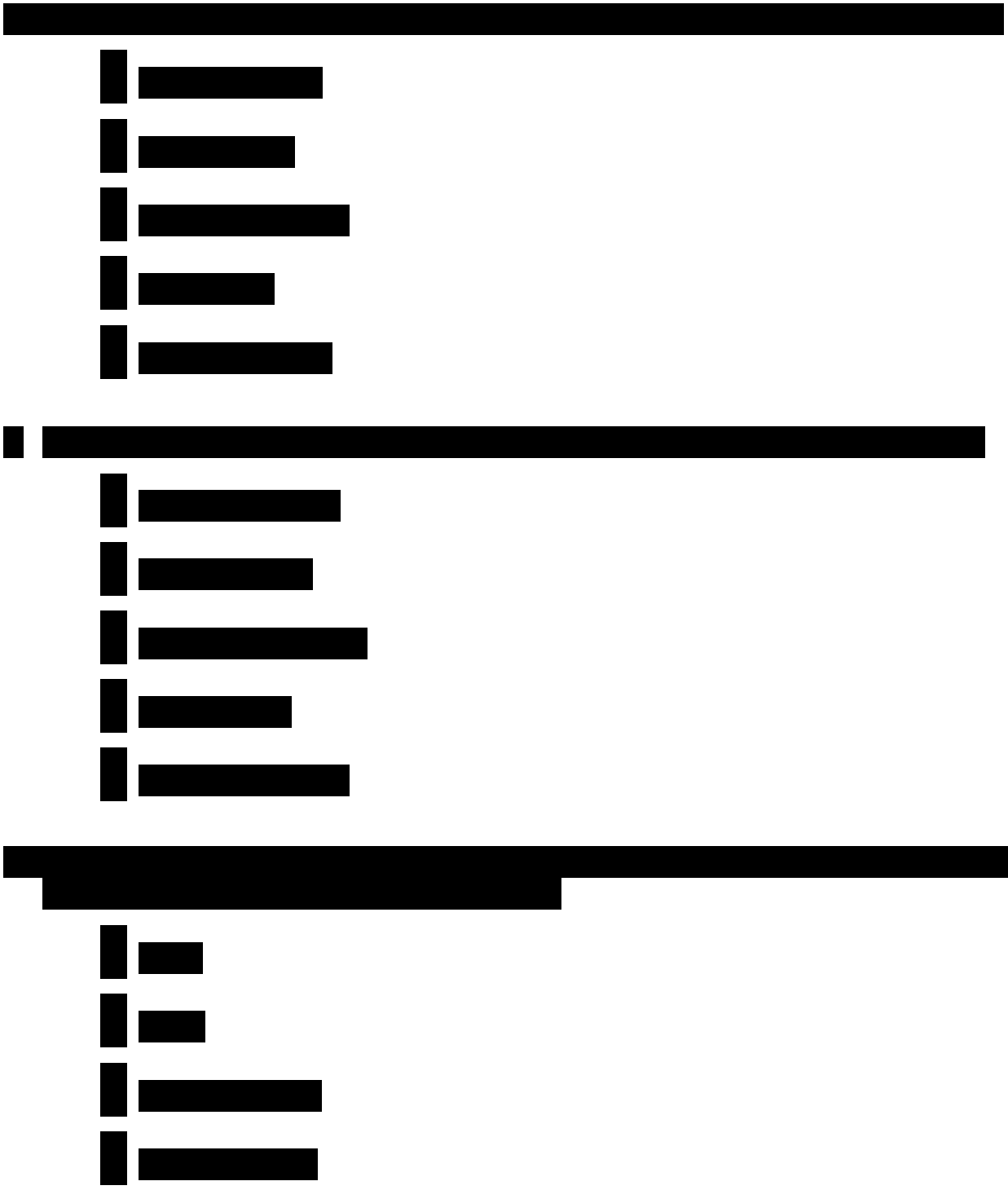
[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]



10.14. [redacted]

[redacted]

10.15. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.16. Appendix 16: Investigator Signature Page

Protocol Title: CoolSculpting® Elite: Multi-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen, Flanks, Upper Arms, Inner Thighs, Outer Thighs, and Submental Area [redacted]

Protocol Number: MED-MA-PLS-0647

Confidentiality and Current GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendment[s], if applicable), 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 participants' state of health will be regarded as confidential. No participants' names will be disclosed. All participants 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 participant before disclosure of participant 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

10.17. References

Beacham BE, Cooper PH, Buchanan CS, Weary PE. Equestrian cold panniculitis in women. Arch Dermatol. 1980;116(9):1025-1027.

Bernstein EF, Bloom JD, Basilavecchio LD, Plugis JM. Non-invasive fat reduction of the flanks using a new cryolipolysis applicator and overlapping, two-cycle treatments. Lasers Surg Med. 2014;46(10):731-735.

Epstein EH Jr, Oren ME. Popsicle panniculitis. N Engl J Med. 1970;282(17):966-967.

Manstein D, Laubach H, Watanabe K, Farinelli W, Zurakowski D, Anderson RR. Selective cryolysis: a novel method of non-invasive fat removal. Lasers Surg Med. 2008;40(9):595-604.

Zelickson B, Egbert BM, Preciado J, Allison J, Springer K, Rhoades RW, Manstein D. Cryolipolysis for noninvasive fat cell reduction: initial results from a pig model. Dermatol Surg. 2009;35(10):1462-1470.