Title Page

Protocol Title: A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Platysma Prominence

Protocol Number: 1936-201-008

Amendment Number: Amendment 1

Product: BOTOX® (botulinum toxin type A) purified neurotoxin complex (United States and Canada adopted name is onabotulinumtoxinA)

Brief Protocol Title: BOTOX for the Treatment of Platysma Prominence

Development Phase: Phase 2

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Refer to the final page of this protocol for electronic signature and date of approval.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	August 2019
Original Protocol	February 2019

Amendment 1 (August 2019)

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in Protocol Amendment 1 was to make the eligibility criteria less restrictive [redacted]

Section No. and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	Make eligibility criteria less restrictive.
Section 10.6, Appendix 6: Study Tabular Summary	[redacted]	To match eligibility criteria.
[redacted]	[redacted]	[redacted]

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[redacted]

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Platysma Prominence

Protocol Number: 1936-201-008

Amendment Number: Amendment 1

Brief Title: BOTOX for the Treatment of Platysma Prominence

Study Rationale:

[redacted]

BOTOX treatment is expected to improve the appearance of platysma prominence by minimizing the visible effects of platysma muscle contraction. The purpose of this placebo-controlled Phase 2 trial is to evaluate the safety and efficacy of a high and a low dose of BOTOX compared with placebo to reduce the appearance of platysma prominence in adult participants with moderate to severe platysma prominence.

Objectives and Endpoints:

Objectives	Endpoints
Primary	**Primary**
• To evaluate the efficacy of a high and low dose of BOTOX compared with placebo in participants with moderate to severe platysma prominence at maximum contraction, as rated by the investigator • To evaluate the safety of a high and low dose of BOTOX compared with placebo in participants with moderate to severe platysma prominence	• Achievement of at least a 1-grade improvement [redacted] at Day 14, as rated at maximum contraction by investigator using the Clinician Allergan Platysma Prominence Scale (C-APPS) • Incidence of adverse events and changes from baseline in vital signs
Secondary	**Secondary**
• To evaluate the efficacy of a high and low dose of BOTOX compared with placebo in participants with moderate to severe platysma prominence at maximum contraction, as rated by the participant	• Achievement of at least a 1-grade improvement [redacted] at Day 14, as rated at maximum contraction by participant using the Participant Allergan Platysma Prominence Scale (P-APPS)

Objectives	Endpoints
Exploratory	**Exploratory**
[redacted]	[redacted]

Overall Study Design:

This is a 4-month, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study to assess the efficacy and safety of single-treatment BOTOX in adult participants with moderate to severe platysma prominence. After verification that the participants have met all inclusion and exclusion criteria, and have completed all baseline study procedures, participants will be randomized in a 1:1:1 ratio to receive BOTOX high dose, BOTOX low dose, or placebo.

There are 8 scheduled study visits: screening (Day -14 to Day -7), randomization/study intervention (Day 1), follow-up visits (Days 7, 14, 30, 60, and 90), and study exit (Day 120).

Number of Participants:

Approximately 165 participants will be enrolled. Based on an anticipated dropout rate of 10%, 148 participants will be analyzable for the primary endpoint.

Number of Sites:

Approximately 15 sites in the United States and Canada

Intervention Groups and Study Duration:

Study participants will be randomized in a 1:1:1 allocation ratio to receive BOTOX high dose, BOTOX low dose, or placebo. [redacted] The highest possible total dose to be administered to a participant is [redacted] U. [redacted]

[redacted]

The total study duration is approximately 4 months.

Data Monitoring Committee: Not applicable

1.2. Schedule of Activities (SoA)

Procedures are recommended to be done in sequence as listed in the schedule below, unless otherwise stated.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7	Visit 8
Study Procedures	**Screening Day -14 to Day -7**	**Baseline/ Randomization/ Intervention Day 1[a]**	**Day 7**	**Day 14**	**Day 30**	**Day 60**	**Day 90**	**Study Exit[b] Day 120**
Visit Windows	-	-	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
Informed Consent, Privacy Authorization	X							
Inclusion/Exclusion Criteria	X	X						
Demographics	X							
Medical/Surgical History	X							
[redacted]	[redacted]							
Weight	X	X	X	X	X	X	X	X
Fitzpatrick Skin Phototype[d]	X							
Abbreviated Physical Examination[e]	X							
Vital Signs[f]	X	X	X	X	X	X	X	X
Urine Pregnancy Test (WOCBP only)[g]	X	X						X
[redacted]	[redacted]	[redacted]						
Standardized Photography	X	X	X	X	X	X	X	X
[redacted]	[redacted]	[redacted]		[redacted]				
Self-Assessment by Participants:								
Participant Allergan Platysma Prominence Scale (P-APPS)[i]		X	X	X	X	X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]						
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visits 7	Visit 8
Study Procedures	**Screening Day -14 to Day -7**	**Baseline/ Randomization/ Intervention Day 1[a]**	**Day 7**	**Day 14**	**Day 30**	**Day 60**	**Day 90**	**Study Exit[b] Day 120**
Visit Windows	**-**	**-**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinician Assessment:								
Clinician Allergan Platysma Prominence Scale (C-APPS)	X	X	X	X	X	X	X	X
Randomization		X						
Study Intervention Administration[j]		X						
Concomitant Medications/Procedures	X	X	X	X	X	X	X	X
Adverse Events[k]	X	X	X	X	X	X	X	X

a All baseline (Day 1) study procedures, including patient-reported outcome questionnaires, must be completed before randomization and study intervention.

b Or early discontinuation from the study. All exit assessments should be completed as soon as possible after a decision to discontinue a participant from the study.

c [redacted]

d Fitzpatrick Skin Phototype is provided in Section 10.11.

e An abbreviated physical examination will be completed at the screening visit and will include the investigator assessment of general appearance, head, ears, eyes, nose, throat (HEENT), and neck.

f Vital Signs (blood pressure, respiratory rate, pulse rate) will be taken while the participant is sitting for at least 5 minutes.

g Woman of childbearing potential (WOCBP) must have a negative urine test result before receiving study intervention. A urine pregnancy test may also be performed at any other visit, at the investigator's discretion.

h [redacted]

[redacted]

j Prepared by an Independent Drug Reconstitutor (IDR) and injected by the investigator. **NOTE**: **The IDR must not perform any other study-related procedures.**

k On Day 1, AEs will be collected prior to and after treatment. Participants will be observed at least 30 minutes after study intervention administration for AEs. In the case of an AESI, see Section 8.3.6.

2. Introduction

Botulinum toxin type A purified neurotoxin (BOTOX®) is approved to treat a variety of medical conditions and was first approved for therapeutic treatment of facial spasmodic disorders in 1989. BOTOX was first approved for aesthetic treatment of glabellar lines in 2002, and today is one of the most popular nonsurgical procedures in aesthetic medicine (ASAPS 2017 Cosmetic Surgery National Data Bank Statistics). When BOTOX is injected into a muscle, it interferes with neuromuscular transmission, producing a temporary chemical denervation resulting in localized relaxation of the muscle and reduction in muscle activity. In the upper face, BOTOX treatment improves the appearance of lines (wrinkles on the skin surface) associated with repeated muscle activity.

[redacted]

BOTOX may be a preferred treatment alternative to cosmetic surgery because its effects are temporary, less invasive with the potential for fewer serious side effects, and not anticipated to require a long recovery time, while producing a relatively rapid, predictable, and desired effect on platysma muscle activity.

[redacted]

A detailed description of the safety and efficacy experience of BOTOX is provided in the IB.

2.1. Study Rationale

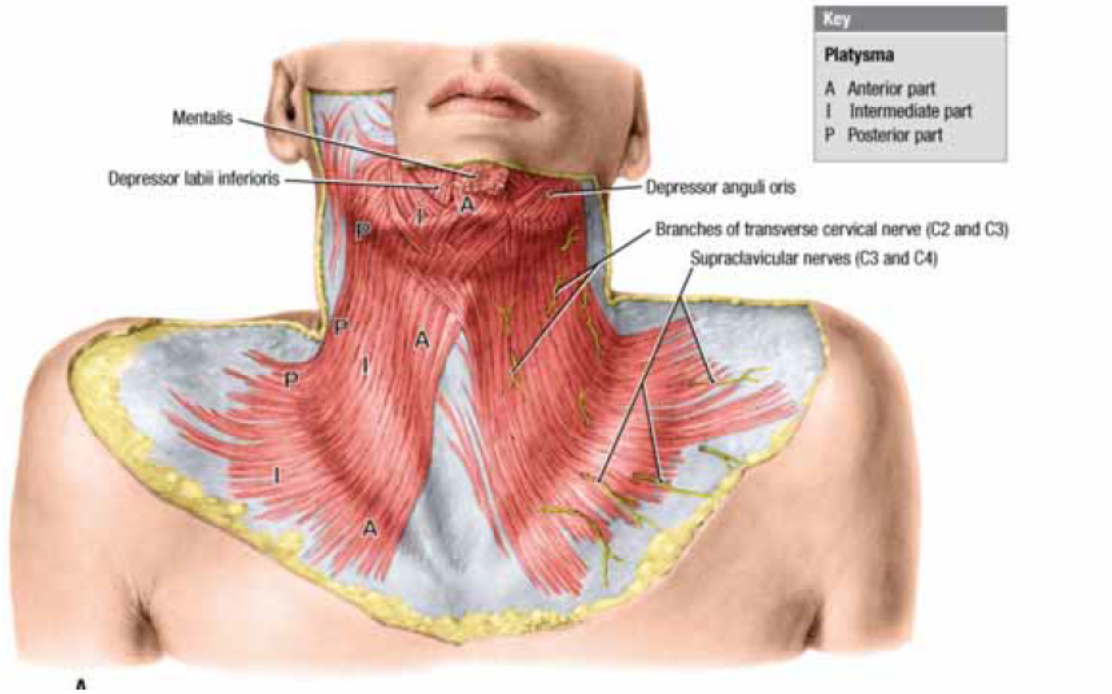
BOTOX treatment is expected to improve the appearance of platysma prominence associated by minimizing the visible effects of platysma muscle contraction.

The purpose of this placebo-controlled Phase 2 trial is to evaluate the safety and efficacy of a high and a low dose of BOTOX compared with placebo to reduce the appearance of platysma prominence in adult participants with moderate to severe platysma prominence.

2.2. Background

[redacted]

Figure 2-1 The Platysma Muscle: Anterior and Posterior Margins of the Platysma Muscle Sheets



Source: Grant's Atlas of Anatomy, 14th Edition

2.3. Benefit/Risk Assessment

[redacted]

[redacted]

More detailed information about the expected benefits and risks and reasonably expected AEs of BOTOX may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	**Primary**
• To evaluate the efficacy of a high and low dose of BOTOX compared with placebo in participants with moderate to severe platysma prominence at maximum contraction, as rated by the investigator • To evaluate the safety of a high and low dose of BOTOX compared with placebo in participants with moderate to severe platysma prominence	• Achievement of at least a 1-grade improvement [redacted] at Day 14, as rated at maximum contraction by investigator using the Clinician Allergan Platysma Prominence Scale (C-APPS) • Incidence of adverse events and changes from baseline in vital signs
Secondary	**Secondary**
• To evaluate the efficacy of a high and low dose of BOTOX compared with placebo in participants with moderate to severe platysma prominence at maximum contraction, as rated by the participant	• Achievement of at least a 1-grade improvement [redacted] at Day 14, as rated at maximum contraction by participant using the Participant Allergan Platysma Prominence Scale (P-APPS)
Exploratory	**Exploratory**
[redacted]	[redacted]

4. Study Design

4.1. Overall Design

This is a 4-month, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study with approximately 165 enrolled participants to assess the efficacy and safety of single-treatment BOTOX in adult participants with moderate to severe platysma prominence. The study will be conducted in the United States and Canada at approximately 15 study sites.

After verification that the participant meets all inclusion and exclusion criteria, and completion of all baseline study procedures, they will be randomized on Day 1. Study participants will be randomized in a 1:1:1 allocation ratio to receive BOTOX high dose, BOTOX low dose, or placebo.

There are 8 scheduled study visits: screening (Day -14 to Day -7), randomization/study intervention (Day 1), follow-up visits (Days 7, 14, 30, 60, and 90), and study exit (Day 120).

Approximately 165 participants will be enrolled. Based on an anticipated dropout rate of 10%, 148 participants will be analyzable for the primary endpoint.

4.2. Scientific Rationale for Study Design

Clinical experience and literature sources suggest that the use of botulinum toxin type A has beneficial effects on platysma prominence. Using a rigorous study design that is randomized, double-blind, and placebo-controlled, this study will provide information regarding the safety and efficacy of BOTOX versus placebo for the treatment of platysma prominence.

The sponsor developed the C-APPS as a clinician's assessment tool for evaluation of platysma prominence at maximum contraction. In the present study, all investigators will be trained to properly use the C-APPS to evaluate and grade the severity of platysma prominence at maximum contraction .

The P-APPS has been developed as a participant self-assessment tool for evaluation of platysma prominence at maximum contraction.

[redacted]

4.3. Justification for Dose

[redacted]

[redacted]

This dose ranging study will evaluate the efficacy and safety of single-treatment BOTOX in adult participants with moderate to severe platysma prominence. Study participants will be randomized in a 1:1:1 allocation ratio to receive BOTOX high dose, BOTOX low dose, or placebo, and study participants could receive up to [redacted] U of BOTOX in this study (Section 6.1).

4.4. End of Study Definition

The End of Study (EOS) Visit is defined as the date of the last visit of the last participant.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

5. Study Population

[redacted] Eligibility criteria for this study are specified in Section 5.1 and Section 5.2.

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 the following criteria apply:

1.	**Age**
1.01	Participant must be at least 18 years of age (or older if legal age of adulthood is > 18 per local regulations) at the time of signing the informed consent
2.	**Type of Participant**
2.01	Participants must have the ability to correctly and maximally contract their platysma muscle
2.02	[redacted]
2.03	[redacted]
3.	**Weight and Body Mass Index**
3.01	[redacted]
4.	**Sex**
4.01	Male or female

5.	**Contraceptives**
5.01	Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period
5.02	A female participant is eligible to participate if she is not pregnant (has a negative urine pregnancy result prior to randomization; see Appendix 7), not breastfeeding, and at least one of the following conditions applies: a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 7 OR b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 7 during the treatment and follow-up period through study exit.
6.	**Informed Consent**
6.01	Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
6.02	Written informed consent from the participant has been obtained prior to any study-related procedures
6.03	Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable
7.	**Other**
7.01	Able, as assessed by the investigator, and willing to read and follow study instructions and likely to complete all study assessments and required study visits

5.2. Exclusion Criteria

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

1.	**Medical Conditions**
1.01	[redacted]

1.02	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
1.05	[redacted]
1.06	Any medical condition that may put the participant at increased medical risk with exposure to BOTOX, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function
1.07	[redacted]
1.08	Participants who have a clinically significant finding or condition (eg, participants with malignancies), any uncontrolled systemic disease or are in a situation which, in the investigator's opinion, may put the participant at significant risk, confound the study results, or interfere significantly with the participant's participation in the study
2.	**Prior/Concomitant Therapy**
[redacted]	[redacted]
	[redacted]

	[redacted]
	[redacted]
[redacted]	[redacted]
2.03	Participant has an anticipated need for treatment with botulinum toxin of any serotype for any indication during the study (other than study intervention)
2.04	[redacted]
2.05	Participant has any planned facial procedure other than standard facial skin care regimen during the study period that, in the opinion of the investigator or designee, may interfere with study assessments
2.06	Anticipated need for surgery or overnight hospitalization during the study
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
4.	**Other**
4.01	[redacted]
4.02	Females who are pregnant, nursing, or planning a pregnancy during the study
4.03	Known immunization or hypersensitivity to any botulinum toxin serotype
4.04	Known allergy or sensitivity to any of the components of the study interventions or any materials used in the study procedures

4.05	History of alcohol or drug abuse within 12 months of the study
[redacted]	[redacted]
[redacted]	[redacted]
4.08	Directly or indirectly involved in the conduct and administration of this study as an investigator, subinvestigator, study coordinator, or other study staff member; or employee of the sponsor or a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study; or enrolled in the study at another clinical site

5.3. Lifestyle Considerations

[redacted]

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the eligibility criteria for participation in this study may be considered for rescreening subject to sponsor's approval. Rescreened participants should be assigned a new participant number.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Study intervention will occur only on Day 1, and participants will not be retreated.

Participants will be observed at least 30 minutes after study intervention administration for AEs.

6.1. Study Intervention Administered

[redacted]

- [redacted]

[redacted]

[redacted]

Table 6-2 Study Formulations and Dilution Instructions

Study Intervention Name	BOTOX High Dose	BOTOX Low Dose	Placebo
[redacted]			
Packaging and Labeling	Each study kit will have one vial containing 100 U of freeze-dried powder. Each vial will be labeled as required per country requirement. The high and low dose BOTOX study kits will look identical.		Placebo vials will be supplied in kits with identical appearance to kits containing BOTOX vials. Each placebo vial will be labeled as required per country requirement.
Manufacturer	Allergan		

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only the sponsor may supply the study intervention; only the Independent Drug Reconstitutor (IDR) may prepare the study intervention; and only the investigator, trained in the study-specific injection technique, may administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The IDR is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Pharmacy Manual.

All unused study intervention and used kits must be returned to the sponsor at the termination of the study. Unit counts will be performed when the study intervention is returned, and all study intervention must be accounted for.

6.3. Measures to Minimize Bias: Randomization and Blinding

At the Screening Visit (Visit 1), after the participant signs the ICF, the site will log on to the IWRS to obtain a participant number. At the time of randomization, eligible participants will be randomly assigned into 1 of the 3 treatment groups in a 1:1:1 allocation ratio to receive either BOTOX high dose, BOTOX low dose, or placebo, respectively (see Section 6.1). The automated IWRS will be used to manage the randomization and treatment assignment based on a randomization scheme prepared by the sponsor. The randomization will occur on Day 1 after all baseline procedures have been completed and the investigator has verified that the participant has met all inclusion and exclusion criteria.

[redacted]

At each study site, designated staff member(s) will serve as the IDR. This person will be unblinded and will be responsible for study intervention preparation and documentation. The IDR must not perform any other study-related procedures; and therefore, will have no role in participant evaluation, data entry, or in any efficacy or safety data collection, analyses, or assessment.

Study intervention will be labeled with kit numbers. The IWRS will provide the IDR with the specific kit number for each randomized participant at the time of randomization (Day 1). The IDR will dispense study intervention according to the IWRS. The IDR will receive the IWRS confirmation notifications for each transaction and will maintain these with the other unblinded study source documents with restricted access to the blinded site study staff. The IDR will prepare the study intervention as described in Table 6-2. Once the study intervention is reconstituted, the IDR will draw the required volume into an appropriately sized syringe and label the syringe with the participant's IWRS assigned ID number (and other information as specified in the Study Pharmacy Manual). All study intervention will be provided in identical syringes to maintain blinding of the study. The IDR will then provide the filled syringes to the investigator, who will inject the participant according to the study treatment administration instructions in Section 6.1.

Blinding is critical to the integrity of the clinical trial. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment of the participant. If a participant's study intervention

assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

6.4. Study Intervention Compliance

Participants will receive a single treatment of BOTOX under the direct supervision of study site personnel.

The study site will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

6.5. Concomitant Therapy

Study center staff must notify the sponsor immediately if a participant consumes any concomitant medications not permitted by the protocol. Participants who admit to using prohibited concomitant medications may be discontinued from the study at the discretion of the investigator or the sponsor.

The use of any concomitant medication or vaccine, (including prescription or over-the-counter medication, vitamins and/or herbal supplements), is to be recorded on the participant's eCRF at each visit along with the reason the medication is taken.

Concomitant therapy and/or medications considered necessary for the study participant's welfare may be given at the discretion of the investigator.

If concomitant medications may have an effect on efficacy or safety outcomes, these medications should be administered in dosages that remain constant throughout the course of the trial at the discretion of the investigator.

If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

6.5.1. Prohibited Interventions and Washout Before the Study

Refer to eligibility criteria (exclusion criteria, Section 5.2).

6.5.2. Permitted Interventions

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication/reason for medication use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific concomitant or prior medication/treatment is in question, please contact the sponsor.

Any medication taken during the study between the date of study intervention and the date of the EOS visit will be recorded in the eCRF as a concomitant medication; any medication started after the EOS visit will not be considered a concomitant medication and should not be captured in the eCRF.

6.5.3. Prohibited Interventions During the Study

The decision to administer a prohibited medication/treatment during the study period is done with the safety of the study participant as the primary consideration. When possible, the sponsor is to be notified before the prohibited medication/treatment is administered.

[redacted]

6.6. Dose Modification

No dose modifications are permitted.

6.7. Intervention after the End of the Study

No interventions after the end of study are planned.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and is randomized 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 in the appropriate eCRF.

The sponsor should be consulted in advance of withdrawal whenever possible. Every effort should be made to retain participants in the study until completion as much as possible. Participants who are withdrawn from the study may not be re-enrolled but will be asked to undergo all early withdrawal activities. Definitions of the standard terms are provided in Appendix 5.

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

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Completed	
Lost to follow-up	
Other	
Physician decision	
Pregnancy	
Protocol deviation	
Screen failure	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

7.1. Discontinuation of Study Intervention

If a participant does not tolerate study injections, the participant will be observed until the intolerability has either resolved or satisfactorily stabilized in the judgement of the investigator and the participant may choose to exit the study or to remain in the study for all safety follow-up assessments through the EOS Visit.

If a pregnancy is confirmed after the participant has received study intervention, the participant may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow-up assessments through the EOS visit.

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.

- 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.
- See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he/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 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will 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.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.2).
- 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 schedule of assessments, 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. During the Screening Period, the investigator or subinvestigator will assess the clinical significance of any physical examination findings. Any participants with abnormalities judged to meet exclusion criteria will be excluded from the study.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

Prior to enrolling participants, investigators (or subinvestigators when applicable) will be trained in grading platysma prominence severity using the C-APPS.

[redacted]

8.1.2. Secondary Efficacy Assessment

[redacted]

[redacted]

[redacted]

[redacted]

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.2).

[redacted]

8.2.2. Vital Signs

Vital signs will be assessed as follows:

Pulse rate, blood pressure, and respiratory rate will be assessed with participants in a sitting position; use of either a manual or automated device is acceptable.

- Pulse rate (beats per minute): Participants are to be seated for at least 5 minutes, and pulse will be counted over 60 seconds and recorded in the source document and eCRF as beats per minute.
- Blood pressure (mm Hg): Participants are to be seated for at least 5 minutes and systolic and diastolic blood pressure will be measured.
- Respiration rate (breaths per minute): Participants are to be seated for at least 5 minutes and breaths will be counted for 30 seconds and multiplied by 2.

8.2.3. Pregnancy Testing

Women of childbearing potential (WOCBP) must have a negative urine test result before receiving study intervention. A urine pregnancy test may also be performed at any other visit, at the investigator's discretion.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver or surrogate).

The investigator and any qualified designees are responsible for collecting, detecting, documenting, and recording events that meet the definition of an AE or SAE and any other study-specific term 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 Adverse Event and Serious Adverse Event Information

All SAEs from the signing of the ICF until the follow-up visit will be collected at the timepoints specified in the SoA (Section 1.2), and as observed or reported spontaneously by study participants.

All AEs from the signing of the ICF until the follow-up visit will be collected at the timepoints specified in the SoA (Section 1.2), and 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.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours of awareness, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

AESIs are described below in Section 8.3.6 and in Appendix 3.

Investigators are not obligated to actively seek 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.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting 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 Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESI (as defined in Section 8.3.6) 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).

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 to elucidate the nature and/or causality of the AE or SAE 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 with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- 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, IRBs/ IECs, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- 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 the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the EOS.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (eg, spontaneous or elective abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

[redacted]

[redacted]

8.3.7. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol, for example:

- Wrong study intervention
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

8.4. Treatment of Overdose

The LD_{50} for BOTOX in humans is estimated from primate studies to be approximately 3000 U. This makes accidental injection of a lethal dose highly unlikely, but significant AEs may still occur at doses below the LD_{50} (Herrero 1967, Scott 1989).

Excessive doses may produce local or distant, generalized, and profound neuromuscular paralysis. Should accidental injection or oral ingestion occur or overdose be suspected, the participant should be medically monitored for up to several weeks for progressive signs or symptoms of systemic muscular weakness that could be local or distant from the site of injection, and which may include ptosis, diplopia, dysphagia, dysarthria, generalized weakness, or respiratory failure.

If the musculature of the oropharynx and esophagus is affected, aspiration may occur, which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care. Additional information is available in the IB.

In the event of an overdose, the investigator should:

1. Contact the sponsor immediately.
2. Closely monitor the participant for any AE/SAE [redacted] and seek medical help as needed.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF as well as other details that led to the overdose.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics are not evaluated in this study.

[redacted]

[redacted]

9.2. Sample Size Determination

[redacted]

Approximately 165 participants will be enrolled in a 1:1:1 randomization allocation ratio, yielding approximately 55 participants in the BOTOX high dose group, 55 participants in the BOTOX low dose group, and 55 participants in the placebo group. [redacted]

[redacted]

9.3. Populations for Analyses

The 2 analysis populations are defined below:

- The mITT population includes all randomized participants with ≥ 1 postbaseline assessment for the primary efficacy endpoint. Participants will be summarized according to the randomized study intervention.

- The safety population includes all randomized participants who are administered study intervention. Participants will be summarized according to the study intervention they received.

9.4. Statistical Analyses

The SAP and PRO SAP for psychometric analysis 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 summarizes the main features of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

9.4.1.1. Primary and Secondary Endpoints

The primary and secondary efficacy endpoints will be analyzed for the mITT population (Table 9-2). All other efficacy endpoints and analyses will be defined in the SAP.

Table 9-2 Primary and Secondary Endpoints

Endpoint	Description	Timing	Methodology
C-APPS Responder (primary endpoint)	Achievement of ≥ 1-grade C-APPS improvement at maximum contraction [redacted] at Day 14	Day 14	Responder
P-APPS Responder (secondary endpoint)	Achievement of ≥ 1-grade P-APPS improvement at maximum contraction [redacted] at Day 14	Day 14	Responder

9.4.1.2. Multiple Comparisons Procedure

The overall FWER will be controlled at $\alpha = 0.05$ for the set of primary and secondary endpoint comparisons between each of the BOTOX groups versus placebo (4 comparisons). The overall serial gatekeeping MCP will be used to control FWER and is defined in Table 9-3.

Table 9-3 Multiple Comparisons Procedure

MCP Step[a]	Endpoint	MCP Criteria
1	C-APPS responder (BOTOX high dose vs placebo)	Nominal p-value ≤ α
2	P-APPS responder (BOTOX high dose vs placebo)	Nominal p-value ≤ α
3	C-APPS responder (BOTOX low dose vs placebo)	Nominal p-value ≤ α
4	P-APPS responder (BOTOX low dose vs placebo)	Nominal p-value ≤ α

[a] Serial gatekeeping MCP only proceeds to next step if all endpoints are statistically significant after application of MCP criteria in previous and current MCP steps for a BOTOX group.

9.4.1.3. Primary and Secondary Analyses

The proportion of responders will be analyzed using CMH tests [redacted]. In addition, 2-sided 95% confidence intervals for the treatment differences in response rates will be provided. Between group comparisons will only be performed for each BOTOX group against the placebo group, and BOTOX high dose group against the BOTOX low dose group.

9.4.2. Safety Analyses

The safety analyses will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs and vital signs. For each safety parameter, the last nonmissing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter.

9.4.2.1. Adverse Events

An AE will be considered a TEAE if:

- The AE began after the first dose of study intervention; or
- The AE was present before the first dose of study intervention, but increased in severity or became serious after the first dose of study intervention

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

The total number and percentage of participants reporting AEs, TEAEs, treatment-related TEAEs, serious TEAEs, treatment-related serious TEAEs, deaths, and discontinuations due to TEAEs will be summarized for each treatment group.

The number and percentage of participants reporting TEAEs in each study intervention group will be tabulated by system organ class, preferred term, and severity.

The number and percentage of participants reporting serious TEAEs in each study intervention group will be tabulated by system organ class and preferred term.

The number and percentage of participants reporting treatment-related TEAEs in each study intervention group will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same PT 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.

The number and percentage of participants reporting TEAEs that are included in the possible distant spread of toxin (PDSOT) term list in each study intervention group will be tabulated by preferred term. The PDSOT term list will be provided by the medical safety physician (MSP).

The PDSOT will be reviewed by the MSP on a monthly basis for monitoring severity, frequency, and trending.

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

The definitions of an AE and SAE can be found in Appendix 3.

[redacted]

9.4.2.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic BP, pulse rate, and respiration rate) at baseline and changes from baseline at each assessment will be presented by study intervention.

9.4.3. Other Analyses

All other exploratory efficacy analyses will be described in the SAP. Psychometric analysis will be performed by a CRO and described in a separate PRO SAP.

9.5. Interim Analyses

Interim analyses are not planned for this study.

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 Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH/ISO/GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, 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 overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators 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 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, HIPAA requirements, where applicable, 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 or the participant's legally authorized representative.
- Participants who are rescreened are not required to sign a new ICF if rescreening occurs within 14 days of first signing the ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records, datasets, or photographs that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- 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.

10.1.5. Posting Clinical Study Data

- Company-sponsored study information and tabular study results will be posted to the US National Institutes of Health website www.clinicaltrials.gov and other publicly accessible sites, if applicable.
- Study data and information may be published in non-promotional, 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.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- 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.

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 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, Good Clinical Practice: Consolidated Guidance and must follow ALCOA, ie, records must be attributable, legible, contemporaneous, original, and accurate.
- Source data are defined as: original documents, data, and records (eg, hospital records, clinical and office charts, diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiche, photographic images, negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study). These records include, but are not limited to, original signed and dated consent forms, relevant

observations including records of AEs, and records of all exposure to study intervention, and data entered directly into an eCOA device.

- The following information should be entered into the participant's source records, including but not limited to:
    - Statement that standardized photographs were taken as appropriate and data images submitted to the designated third-party vendor
    - Pregnancy test results for WOCBP

10.1.8. Study and Site Closure

The sponsor 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 development of study intervention

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- 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. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. **AE of Special Interest (AESI)** An AESI is an AE of scientific and medical concern specific to the sponsor's study drug/device 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. Dysphagia, dyspnea, aspiration, and aspiration pneumonia have been identified as AESIs for the study intervention in this protocol. Upon identification and awareness of 1 or more of these events, the investigator must document and report the event by completing an AE eCRF, and must notify the MSP and assigned Regional Site Manager by email or phone call within 72 hours of awareness. The SAE/AESI form is not needed unless the AESI is serious. If the AESI meets SAE criteria (which are listed below), it will be reported within 24 hours of awareness per the sponsor's SAE reporting requirements (described below).

Events <u>Meeting</u> the AE Definition
• Any safety assessments (eg, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).The test result is considered to be an AE by the investigator or sponsor. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.
- The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE 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 or SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. 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.
- 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.

Assessment of Intensity

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 of 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 or SAE. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than 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 IB and/or product information, for marketed products, in his/her assessment. • For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE 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. 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.** • 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.

Reporting of SAEs

SAE Reporting
• Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.4. Appendix 4: Abbreviations

3D	3-dimensional
AE	adverse event
[redacted]	[redacted]
ALCOA	attributable, legible, contemporaneous, original, and accurate
[redacted]	[redacted]
[redacted]	[redacted]
BOTOX	botulinum toxin type A purified neurotoxin
BP	blood pressure
C-APPS	Clinician Allergan Platysma Prominence Scale
CDISC	Clinical Data Interchange Standards Consortium
CFR	code of federal regulations
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CRO	contract research organization
eCOA	electronic clinical outcomes assessment (via tablet)
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
FWER	familywise error rate
GCP	good clinical practice
HEENT	head, eyes, ears, nose, throat
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IDR	independent drug reconstitutor
IEC	independent ethics committee
IND	Investigational New Drug

BOTOX	
IRB	institutional review board
ISO	International Organization for Standardization
IWRS	Interactive Web Response System
MCP	multiple comparisons procedure
mITT	modified intent-to-treat
MSP	medical safety physician
NCI	National Cancer Institute
P-APPS	Participant Allergan Platysma Prominence Scale
PDSOT	possible distant spread of toxin
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO	patient reported outcome
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
WOCBP	woman of childbearing potential

10.5. Appendix 5: 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
Adverse event	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 serious adverse event, 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)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
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)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (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)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

This table is intended for use in posting study information to registries (eg, ClinicalTrials.gov).

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Platysma Prominence
	Clinical Study Sponsor	Allergan Sales LLC
	Trial Phase Classification	Phase 2
	Trial Indication	Platysma Prominence
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	Approximately 4 months
	Planned Country of Investigational Sites	United States and Canada
	Planned Number of Subjects	165
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Diagnosis Group	Adults with moderate to severe platysma prominence
	Healthy Subject Indicator	Yes
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	No upper age limit
	Sex of Participants	Male or Female
	Stable Disease Minimum Duration	Not applicable

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	OnabotulinumtoxinA
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	Neurotoxin
	Dose per Administration	Up to [redacted] U
	Dose Units	U
	Dosing Frequency	Single-treatment on Day 1
	Route of Administration	Intramuscular
	Current Therapy or Treatment	Not applicable
	Added on to Existing Treatments	No
	Control Type	Placebo
	Comparative Treatment Name	Not applicable
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	3
	Trial is Randomized	Yes
	Randomization Quotient	1:1:1 (BOTOX high dose:BOTOX low dose:placebo)
	Trial Blinding Schema	Double blind
	[redacted]	[redacted]
	Adaptive Design	No
	Study Stop Rules	Not applicable

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

   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 follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Contraception Guidance:

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method 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 • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Etonogestrel implant (ie, Nexplanon®) Bilateral tubal occlusion 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.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive pregnancy test at screening and also a negative test on Day 1.
- Additional pregnancy testing may also be performed at any other study visit at the investigator's discretion and at the study exit visit, and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

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. 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. A spontaneous or elective abortion is always considered to be an SAE and will be reported as such. Any poststudy 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.
- If a pregnancy is confirmed after the participant has received study intervention, the participant may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow-up assessments through the end-of-study visit.

10.8. Appendix 8: Clinician Allergan Platysma Prominence Scale

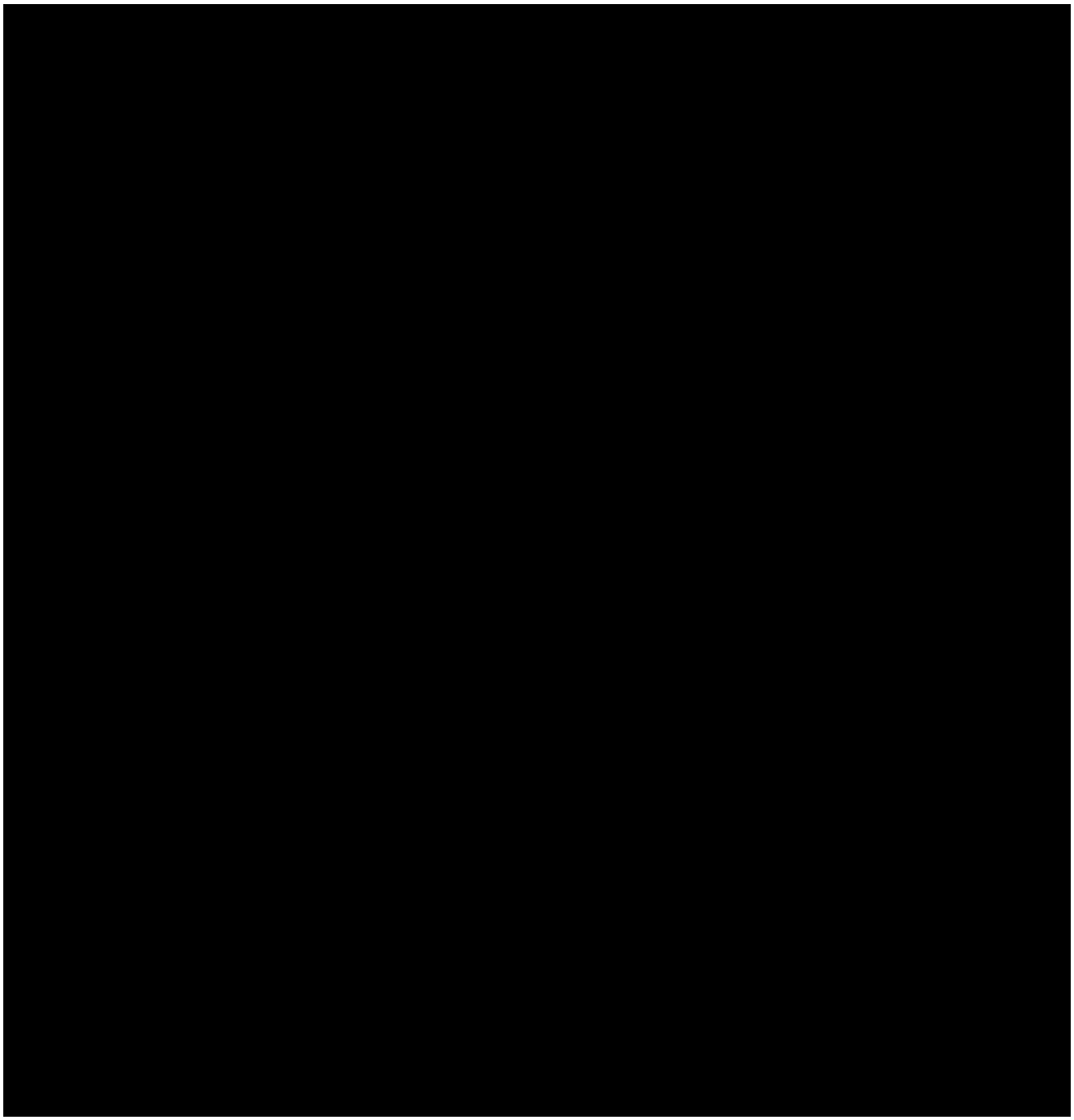
C-APPS grades and descriptions are shown in Section 8.1.1, Table 8-1.

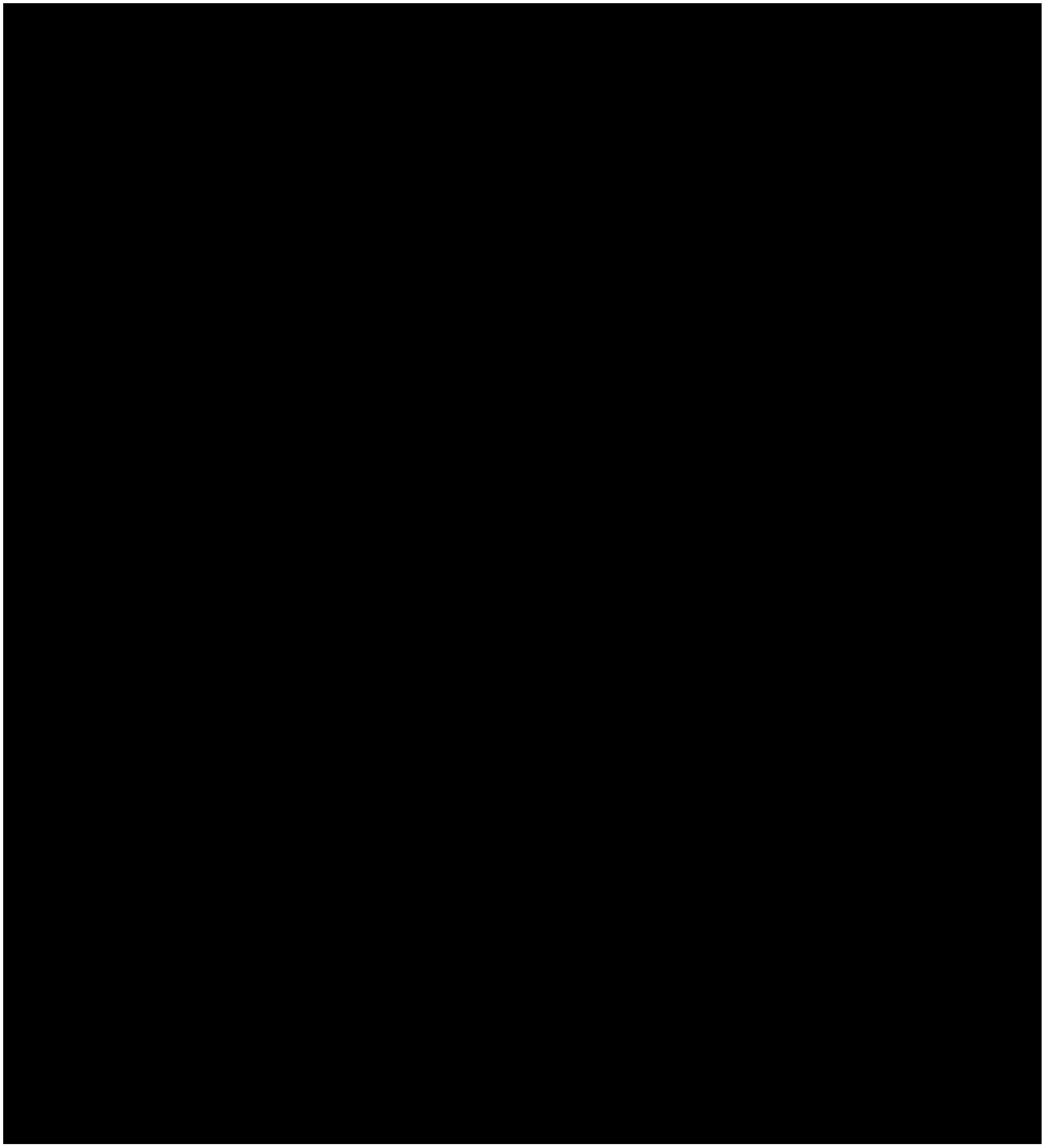
10.9. [redacted]

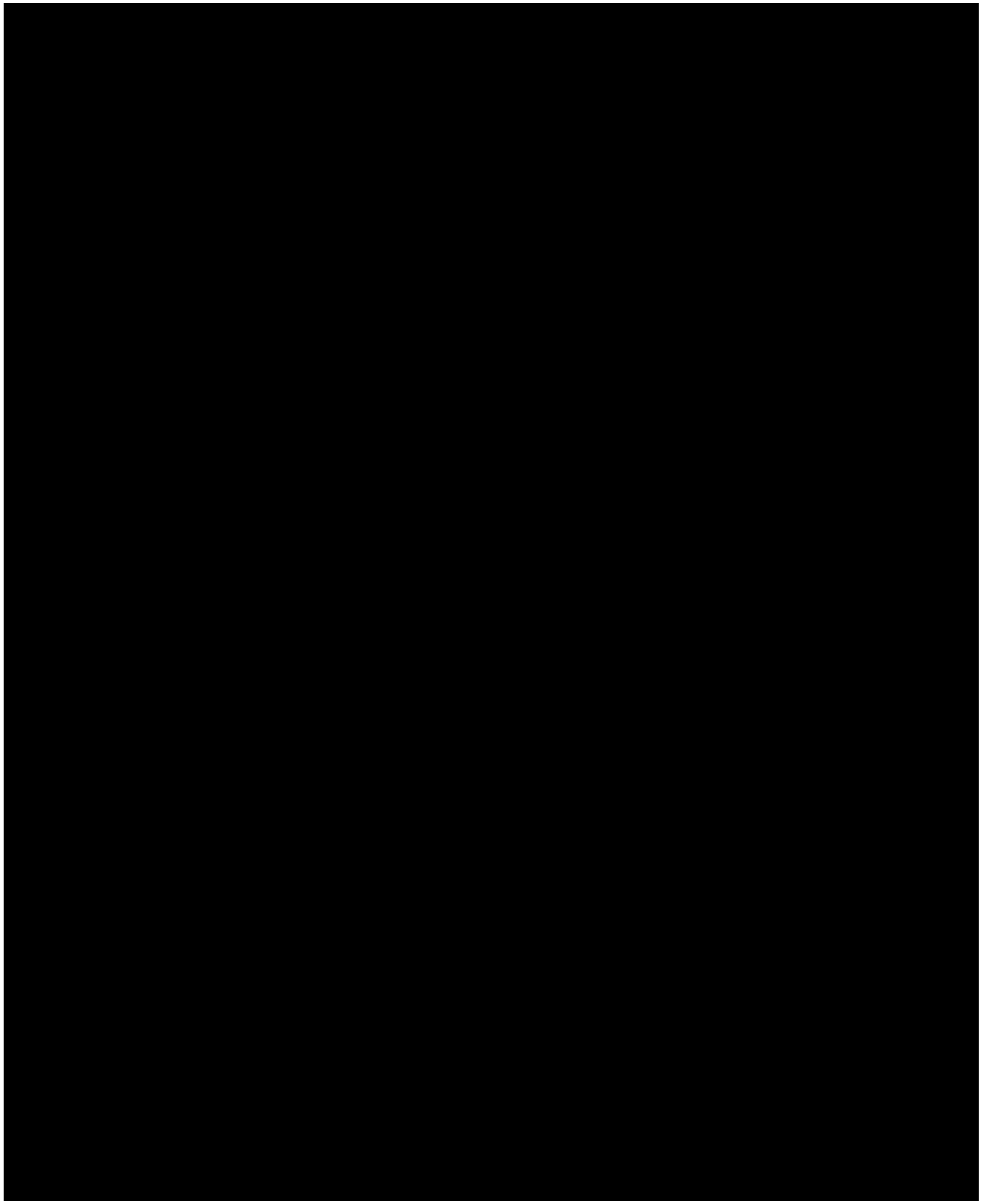
[redacted]

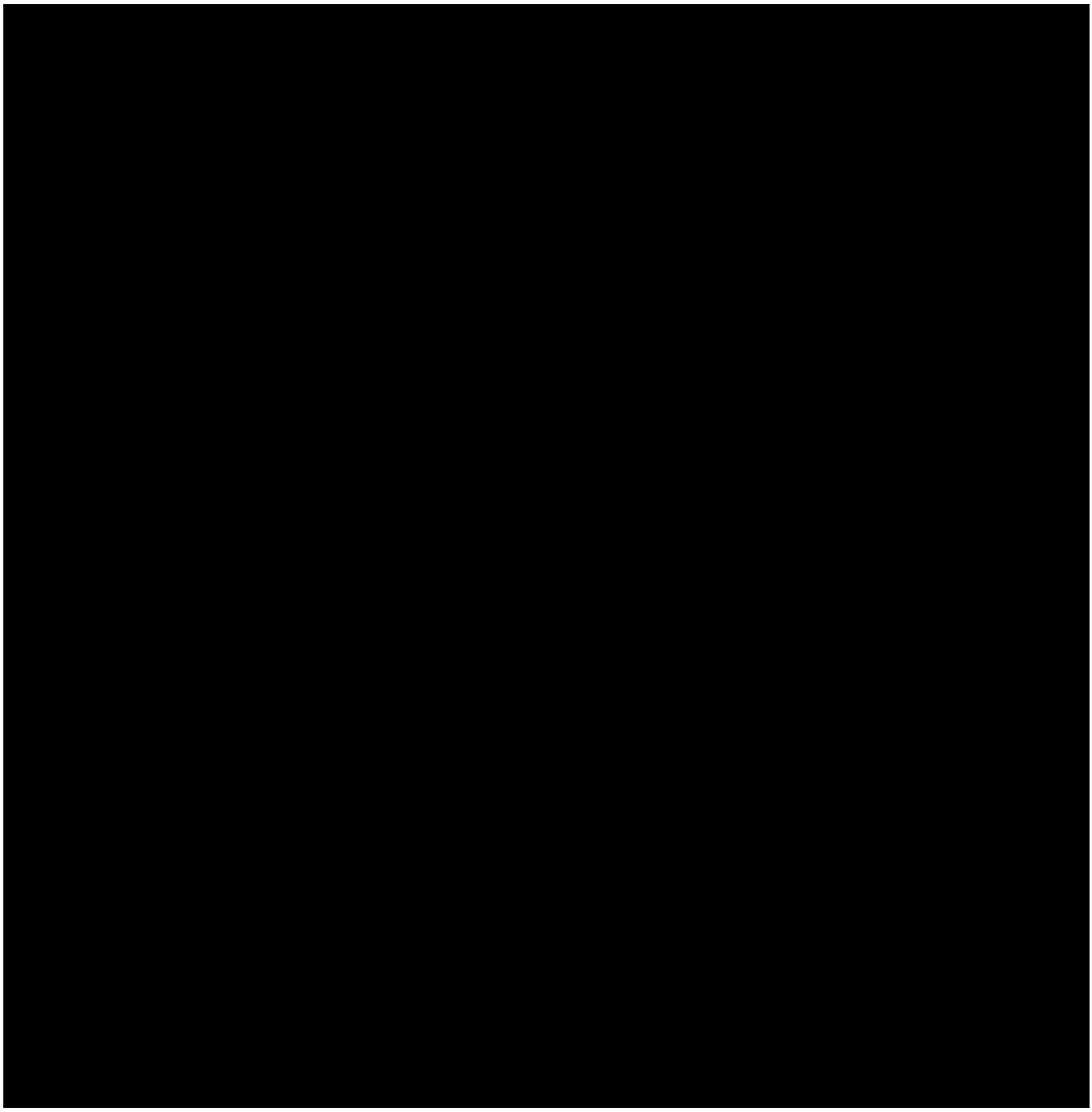
10.10. Appendix 10: Example Patient-Reported Outcomes Questionnaires, Descriptions, and Instructions

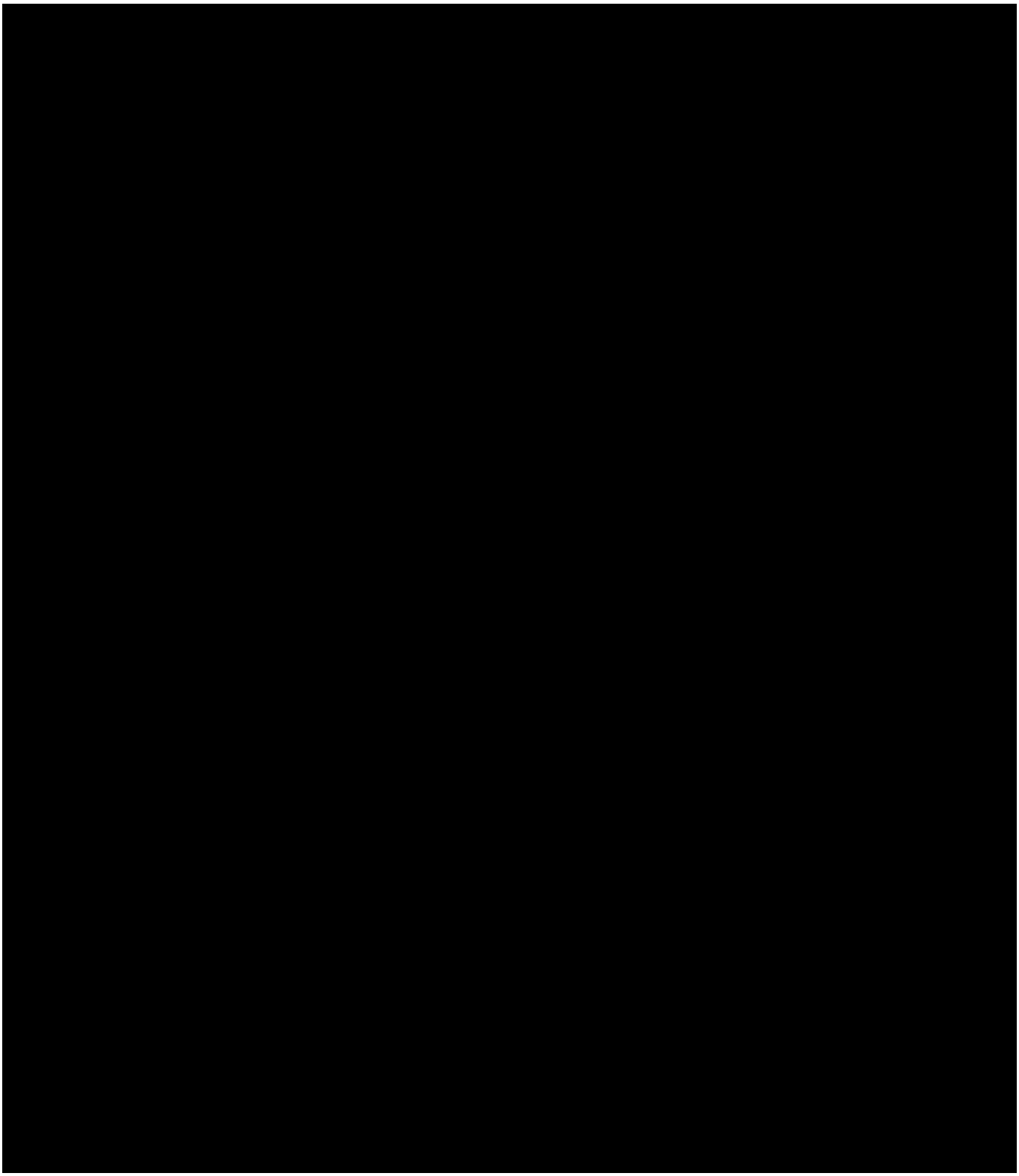
This appendix provides complete samples of each questionnaire; however, participants will provide responses in electronic tablets (ie, eCOA) at the site.

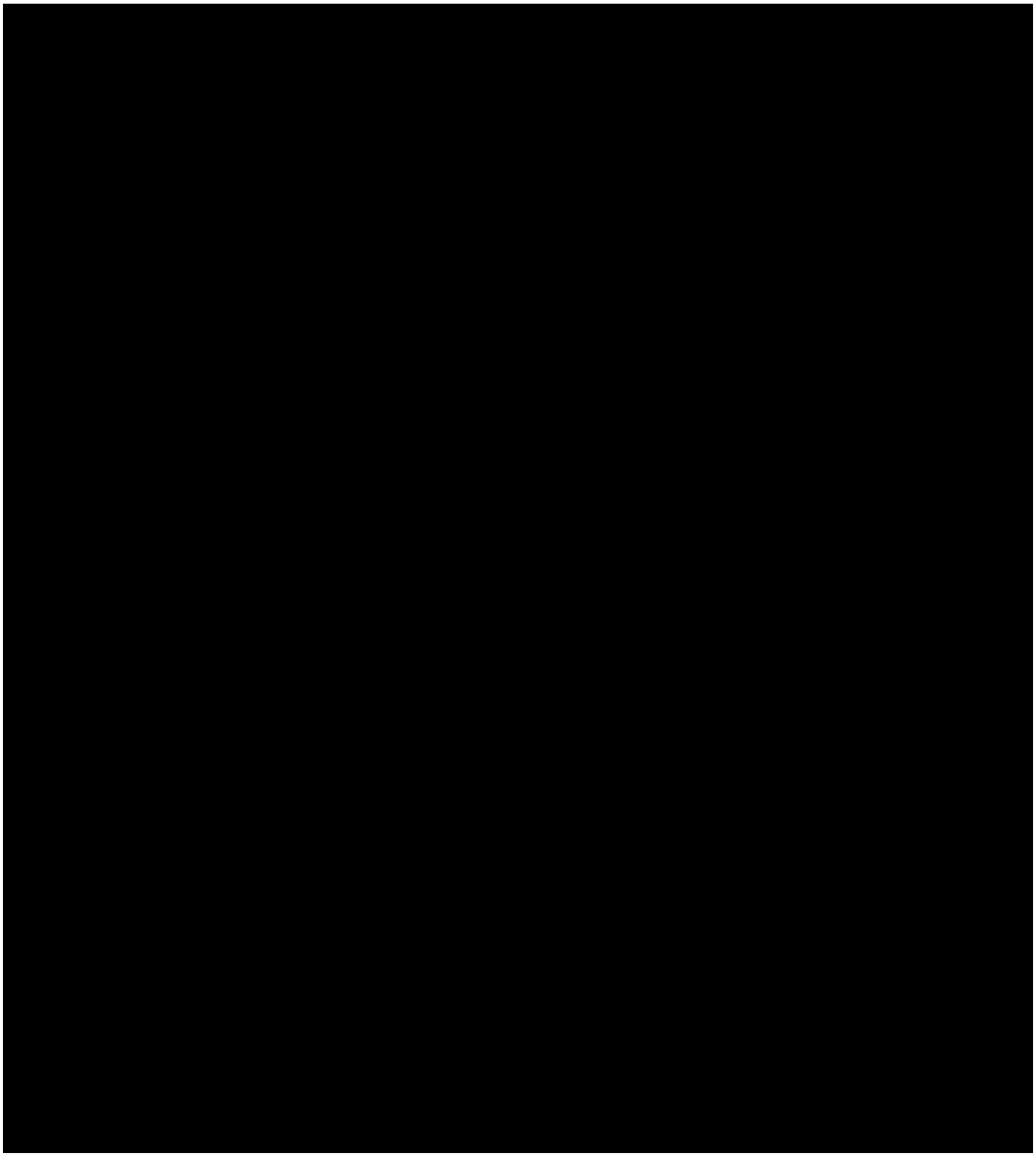


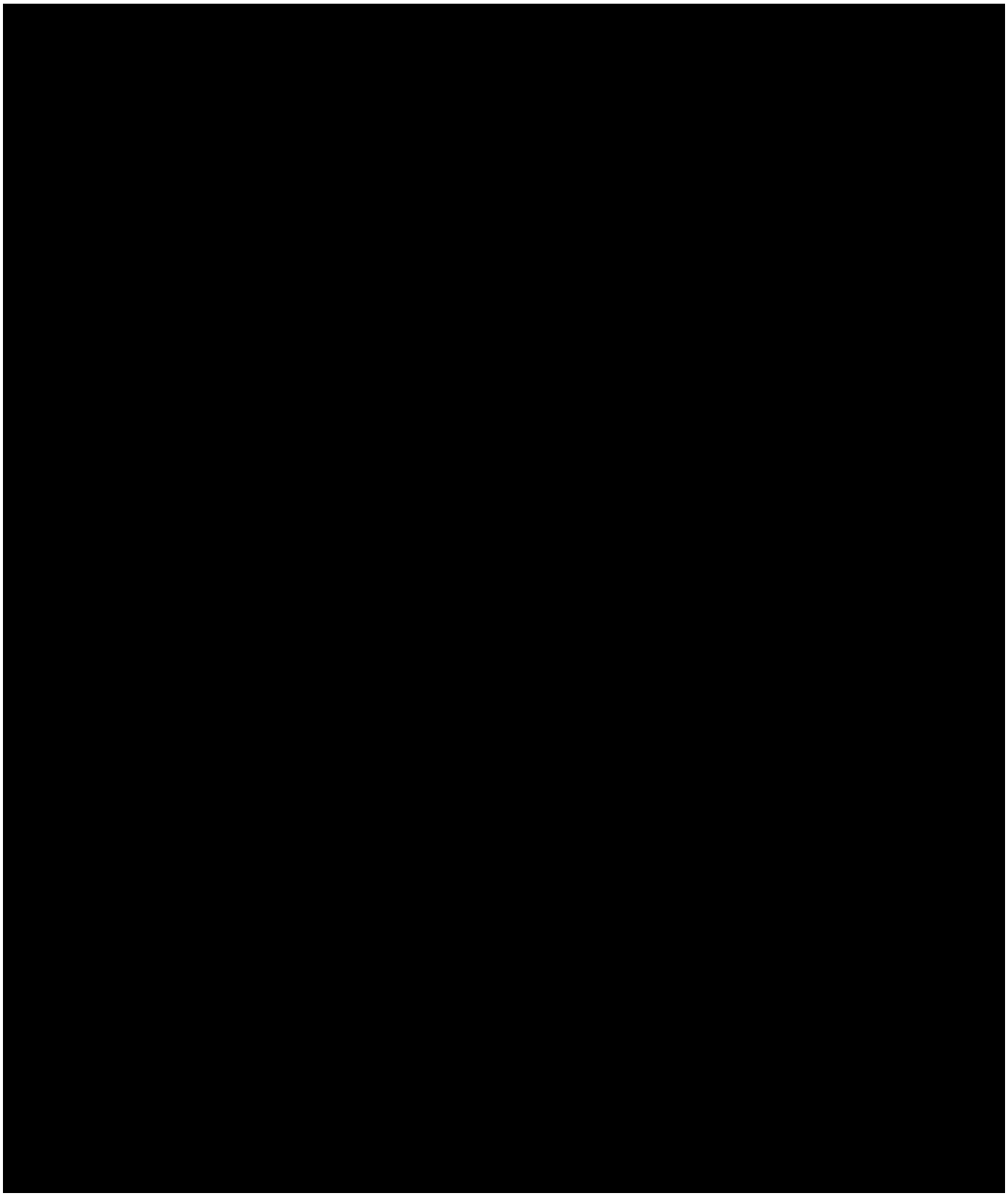


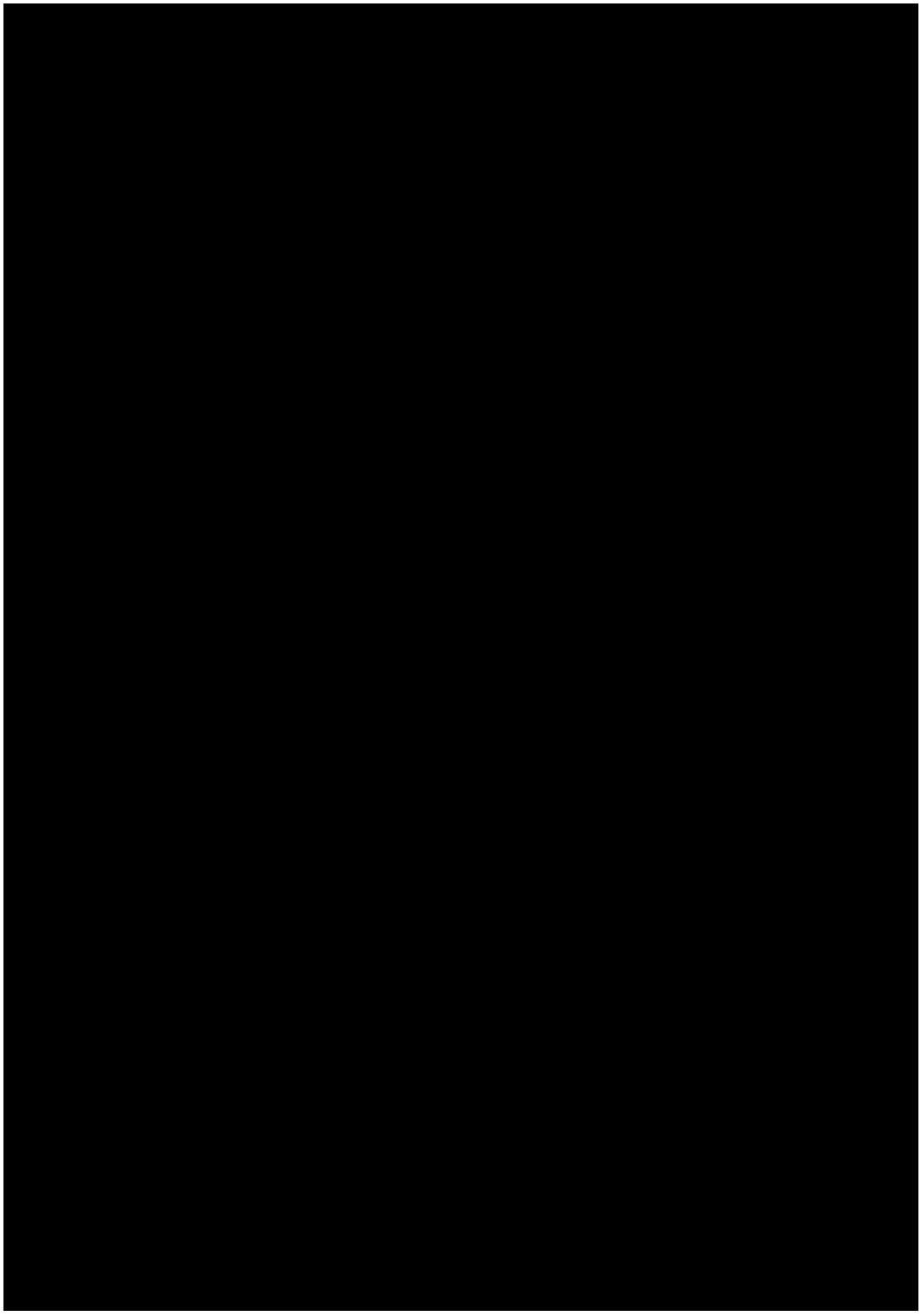


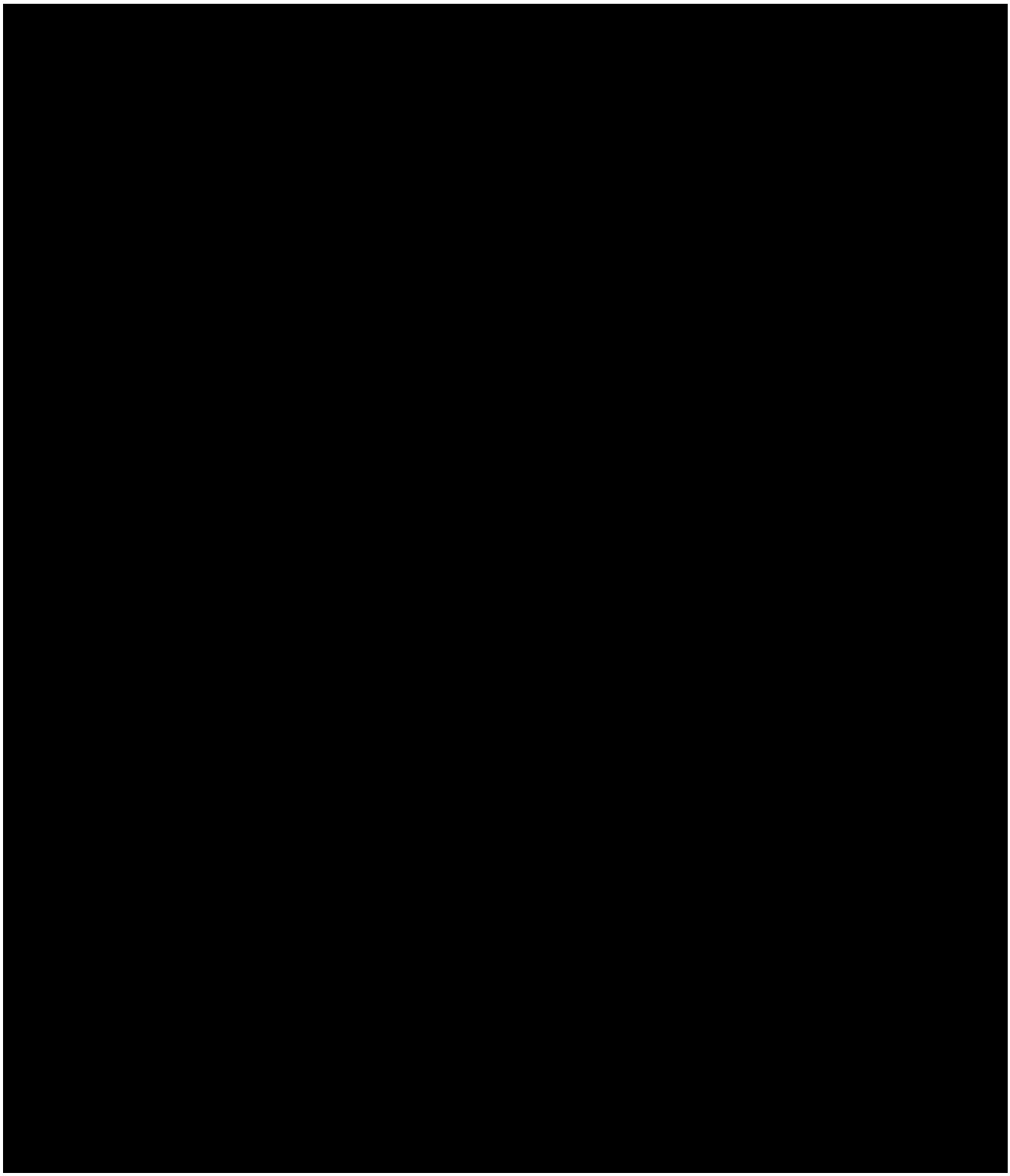


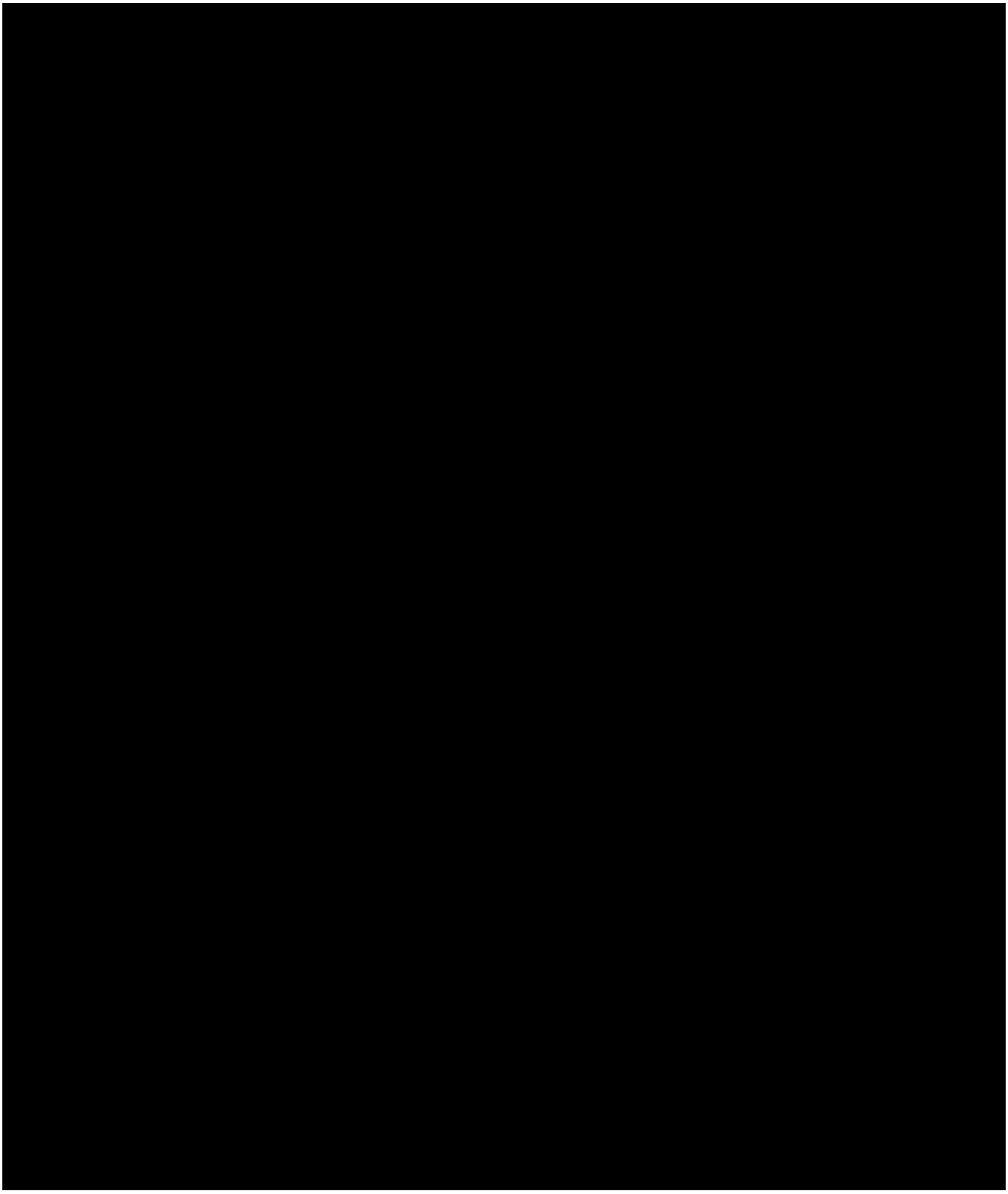












10.11. Fitzpatrick Skin Phototype

Type	Description
I	Always burns easily; never tans (sensitive)
II	Always burns easily; tans minimally (sensitive)
III	Burns moderately; tans gradually (light brown) (normal)
IV	Burns minimally; always tans well (moderate brown) (normal)
V	Rarely burns; tans profusely (dark brown) (insensitive)
VI	Never burns; deeply pigmented (insensitive)

Source: Federal Register 1999

11. References