1 STUDY TITLE

A Prospective, Multicenter, Randomized, Masked, Controlled Clinical Study to Evaluate the Safety and Performance of the enVista® One-Piece Hydrophobic Acrylic Trifocal Intraocular Lens in Subjects Undergoing Cataract Extraction

CLINICAL STUDY PROTOCOL
STUDY # 900

Developmental phase of study:	Pivotal ITA Trial
Study design:	Prospective, multicenter, randomized, controlled, binocular safety and performance study
Date:	09 October 2019, Version 1.0 11 March 2020, Version 2.0 06 July 2020, Version 3.0 05 February 2021, Version 4.0 15 April 2021, Version 5.0
Sponsor[1]	Bausch & Lomb, Inc., a division of Bausch Health Americas, Inc. 400 Somerset Corporate Boulevard Bridgewater, NJ 08807

This clinical investigation is being conducted in accordance with EN ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, and generally in accordance with EN ISO 11979-7:2018 Ophthalmic implants — Intraocular lenses — Part 7: Clinical Investigations of Intraocular Lenses for the Correction of Aphakia, ISO/TR 22979:2017 Ophthalmic implants – Intraocular lenses – Guidance on assessment of the need for clinical investigation of intraocular lens design modifications, ANSI Z80.12-2007 (R2017), Medical Device Regulation 2017/745, and applicable local regulations and standards.

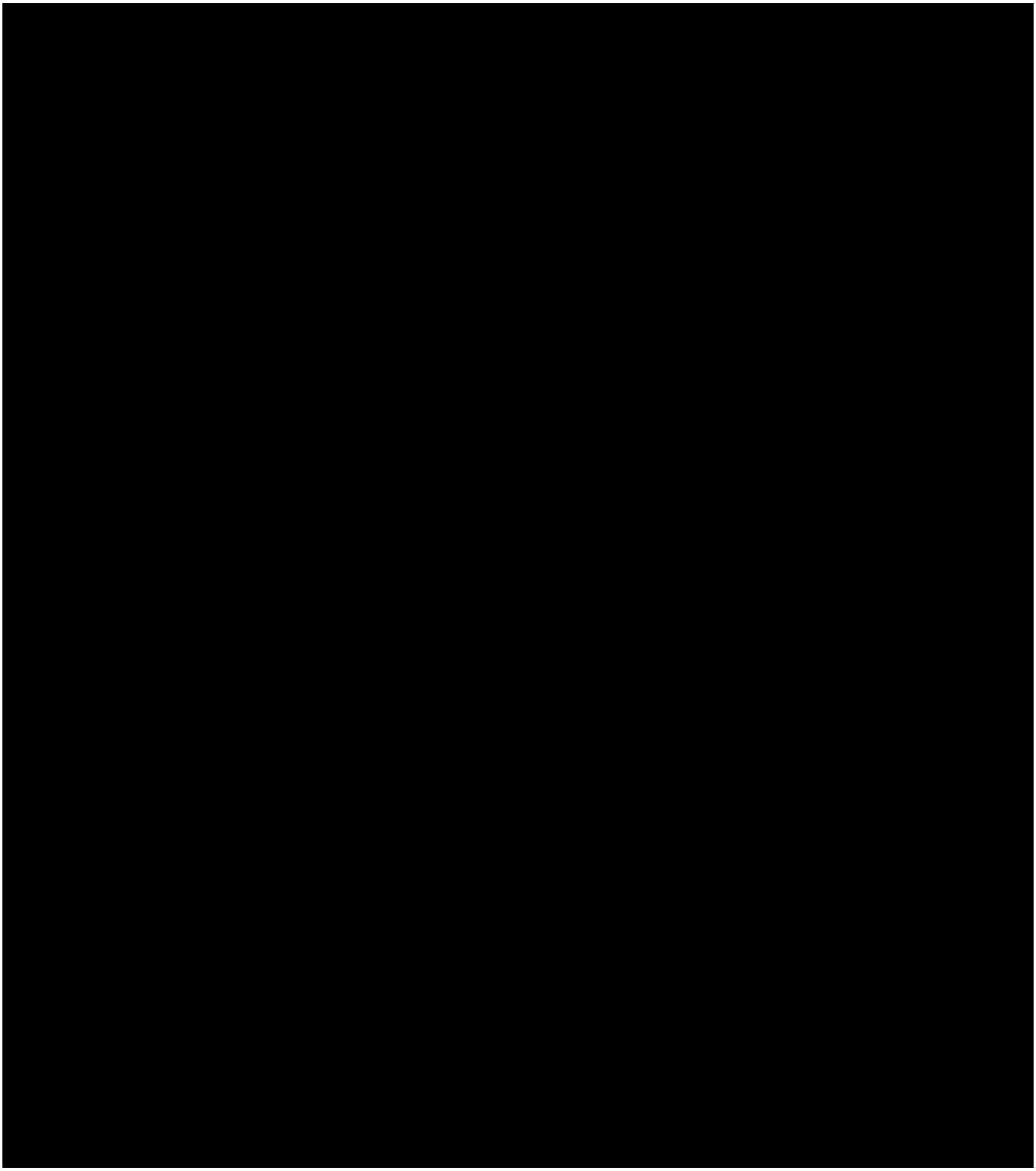
CONFIDENTIAL

Nothing herein is to be disclosed without prior approval of the Sponsor.

[1] The Sponsor, Bausch & Lomb, Inc., is the sole funding source for this clinical investigation.

Protocol Review and Approvals

A Prospective, Multicenter, Randomized, Masked, Controlled Clinical Study to Evaluate the Safety and Performance of the enVista® One-Piece Hydrophobic Acrylic Trifocal Intraocular Lens in Subjects Undergoing Cataract Extraction



Personnel Responsible for Conducting the Study

A Prospective, Multicenter, Randomized, Masked, Controlled Clinical Study to Evaluate the Safety and Performance of the enVista® One-Piece Hydrophobic Acrylic Trifocal Intraocular Lens in Subjects Undergoing Cataract Extraction

Contract Research Organization (CRO) / Medical Monitor/External Consultant

Personnel Responsible for Conducting the Study

A Prospective, Multicenter, Randomized, Masked, Controlled Clinical Study to Evaluate the Safety and Performance of the enVista® One-Piece Hydrophobic Acrylic Trifocal Intraocular Lens in Subjects Undergoing Cataract Extraction

Contract Research Organization (CRO) / Medical Monitor/External Consultant

Investigative Clinical Sites[2]

Site Contact List, provided as an attachment to the study reference manual

[2] All contractual and financial agreements between clinical sites and the Sponsor will be administrated by the CRO designated by the Sponsor and approved at a minimum by both Investigators and the Sponsor in writing. See Section 13.4.

Principal Investigator Protocol Agreement Page

INVESTIGATOR'S AGREEMENT IN ACCORDANCE WITH SUBSECTION 81(k) OF THE *MEDICAL DEVICES REGULATIONS*

Device Name/Nom de l'instrument:_____

Protocol Number/N° du Protocole:_____

I, _____,
undertake, as outlined in Subsection 81(k) of the *Medical Devices Regulations,* to:

(i) conduct the investigational testing in accordance with the protocol:

_____
_____
_____

(ii) inform a patient who is to be diagnosed or treated with the device of the risks and benefits associated with its use and obtain the written consent of the patient,

(iii) not use the device or permit it to be used for any purpose other than the investigational testing specified in the protocol,

(iv) not permit the device to be used by any person other than myself, except under my direction,

(v) in the event of an incident that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use and has lead to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur, report the incident and the circumstances surrounding it to the Director and the manufacturer or importer of the device, within 72 hours after its discovery.
(Tel: (613) 957-4587 Fax: (613) 957-7318)

Je, _____,
m'engage conformément à la section 81(k) du *Règlement sur les instruments médicaux*, comme decrits ci-bas, à:

(i) effectuer l'essai expérimental conformément au protocole:

_____
_____
_____

(ii) informer le patient qui fera l'objet du diagnostic ou du traitement au moyen de l'instrument des risques et des avantages que comporte son utilisation et obtiendra son consentement écrit,

(iii) ne pas utiliser l'instrument ni n'en permettre l'utilisation à des fins autres que l'essai expérimental décrit dans le protocole,

(iv) ne pas permettra que l'instrument soit utilisé par une personne autre que moi, sauf sous ma direction,

v)advenant un incident qui d'une part, est lié à une défaillance de l'instrument, une dégradation de son efficacité ou un étiquetage ou mode d'emploi défectueux; d'autre part a entraîné la mort ou une détérioration grave de l'état de santé d'un patient, utilisateur ou autre personne, ou serait susceptible de le faire s'il se reproduisait, rapporter l'incident en question de même que les circonstances s'y rapportant, au Directeur et au fabriquant, ou à l'importateur de l'instrument, et ce, en deçà de 72 heures après la découverte de l'incident.
(Tel: (613) 957-4587 Fac: (613) 957-7318)

_____ _____
Signature **Date**

2 Synopsis

Name of Sponsor/Company: Bausch & Lomb, Inc., a division of Bausch Health Americas, Inc.
Name of Investigational Device: enVista® MX60EFH Trifocal Intraocular Lens
Title of Study: A Prospective, Multicenter, Randomized, Masked, Controlled Clinical Study to Evaluate the Safety and Performance of the enVista® One-Piece Hydrophobic Acrylic Trifocal Intraocular Lens in Subjects Undergoing Cataract Extraction
Number of clinical centers: Up to approximately twelve (12) clinical centers in Canada
Objectives: To evaluate the safety and performance of the enVista trifocal intraocular lens (IOL) when implanted in the capsular bag of the eye in adult patients for the visual correction of aphakia following removal of a cataractous lens to provide improved intermediate and near visual acuity, while maintaining comparable distance visual acuity.
Methodology: The study purpose, procedures, and subject responsibilities will be explained to the potential participant. The subject's willingness and ability to meet the treatment and follow-up requirements will be determined. Written informed consent will be obtained from each study subject prior to performing any study-specific procedures, those which are not part of the Investigator's routine standard of care. Subjects who meet eligibility criteria will be randomly assigned to Group 1 (Test enVista MX60EFH trifocal IOLs) or Group 2 (Control enVista MX60E monofocal IOLs) in a 2:1 ratio. All subjects will have their assigned Group IOLs implanted bilaterally. Approximately one hundred sixty-eight (168) subjects implanted bilaterally (336 eyes) will be randomized in this study to obtain complete follow-up for 4-6 months on at least a total of 150 Test and Control IOL subjects, assuming a 10% drop-out rate. This corresponds to at least 200 Test IOL eyes and 100 Control IOL eyes implanted with Test or Control IOLs and completing 4-6 months of post-surgical follow-up. Enrollment and subject assignment to a randomized treatment group (enVista MX60EFH trifocal IOL or enVista MX60E monofocal IOL) will occur following subject signing of the Informed Consent form at Preoperative Visit (Day -30 to Day -5) and confirmation of subject eligibility through review of the study inclusion and exclusion criteria at Preoperative Visit and again at Study Visit 00A (Day 0). All subjects will undergo bilateral implantation of the enVista MX60EFH trifocal IOL or the enVista MX60E monofocal IOL. The first eye implanted with an enVista trifocal or monofocal IOL will be designated eye A and the second eye implanted will be designated eye B. The eye with the worse best-corrected distance visual acuity (CDVA) at the Preoperative Visit will be treated first (eye A) and used in the primary monocular evaluations. If CDVA is the same for both eyes, the right eye will be treated first. Postoperatively, all eyes will undergo ophthalmic examinations at regular intervals per the study visit schedule through Visit 4 (Day 120 to Day 180 after second eye IOL implantation).

Enrolled subjects who meet eligibility criteria will be seen at 10 visits according to the following schedule:

Schedule of Study Visits

Visit Name	Eyes Evaluated	Visit Window
Preoperative Visit 0A/B	Both Eyes	Day -30 to -5
Operative Visit 00A	1st Eye	Day 0
Post-Operative Visit 1A	1st Eye	Day 1 to 2 post Visit 00A
Post-Operative Visit 2A	1st Eye	Day 7 to 14 post Visit 00A
Post-Operative Visit 3A	1st Eye	Day 30 to 60 post Visit 00A
Operative Visit 00B	2nd Eye	Day 7 to 30 post Visit 00A
Post-Operative Visit 1B	2nd Eye	Day 1 to 2 post Visit 00B
Post-Operative Visit 2B	2nd Eye	Day 7 to 14 post Visit 00B
Post-Operative Visit 3B	2nd Eye	Day 30 to 60 post Visit 00B
Post-Operative Visit 4	Both Eyes	Day 120 to Day 180 post Visit 00B

Ophthalmic measurements of CDVA and UDVA will be done at 4 meters unless otherwise described in the protocol. Measurements of DCNVA and UNVA will be done as described in the protocol at 40 cm. Similarly, measurements of DCIVA and UIVA will be done as described in the protocol at 66 cm.

Number of Subjects Planned: Approximately 168 subjects implanted bilaterally (336 eyes) will be enrolled at up to approximately 12 clinical sites and will have two cataractous lenses removed according to the timing provided in the Table above and replaced with two enVista trifocal intraocular lenses (IOLs) or two enVista monofocal IOLs of the same material.

Diagnosis and Criteria for Inclusion:

This study will include subjects who meet the following inclusion criteria:

1. Subjects must be 18 years of age or older on the date the Informed Consent Form (ICF) is signed.
2. Subjects must have the capability to understand and provide written informed consent on the Institutional Review Board (IRB) /Independent Ethics Committee (IEC) -approved Informed Consent Form (ICF) and authorization as appropriate for local privacy regulations.
3. Subjects must have a clinically significant cataract (cortical, nuclear, subcapsular, or combination) as determined by the medical judgment of the Investigator, in each eye that is considered amenable to treatment with standard phacoemulsification cataract extraction and capsular IOL implantation, with CDVA equal to or worse than 20/40 in at least one eye, with or without a glare source.
4. Subjects must have a CDVA projected to be equal to or better than 20/32 after IOL implantation in each eye, as determined by the medical judgment of the Investigator or measured by potential acuity meter (PAM) testing, if necessary.
5. Subjects must have clear intraocular media other than the cataract in both eyes.
6. Subjects must have discontinued use of contact lenses for at least 2 weeks (for hard or toric lenses) or 3 days (for soft lenses) prior to the pre-operative examination and must be willing to refrain from use of contact lenses throughout the clinical study.
7. Contact lens wearers must demonstrate a stable refraction (within ±0.50 D for both sphere and cylinder) in both eyes, as determined by distance manifest refraction on two consecutive examination dates after discontinuation of contact lens wear.
8. Subjects must require an IOL power from +16.0 diopter (D) to +27.0 D in both eyes.

9. Subjects must be willing and able to comply with all treatment and follow-up study visits and procedures, and to undergo second eye surgery within 7-30 days of the first eye surgery.

Exclusion Criteria:

This study will exclude subjects (or eyes) who meet any of the following exclusion criteria:

1. Subjects who have used an investigational drug or device within 30 days prior to entry into this study and/or will participate in another investigation during the period of study participation.
2. Subjects who have any corneal pathology (e.g., significant scarring, guttata, inflammation, edema, dystrophy, etc.) in either eye.
3. Subjects who have significant anterior segment pathology that might increase intraoperative risk or compromise IOL stability (e.g., pseudoexfoliation syndrome, synechiae, iris atrophy, traumatic cataract, lens subluxation, traumatic zonulolysis, zonular dialysis, evident zonular weakness or dehiscence, hypermature or brunescent cataract, etc.) in either eye.
4. Subjects who have uncontrolled glaucoma in either eye.
5. Subjects who have previous retinal detachment or clinically significant retinal pathology involving the macula in either eye.
6. Subjects who have proliferative or non-proliferative diabetic retinopathy in either eye.
7. Subjects who have a congenital ocular anomaly (e.g., aniridia, congenital cataract) in either eye.
8. Subjects with instability of keratometry or biometry measurements.
9. Subjects using any systemic or topical drug known to interfere with visual performance, pupil dilation, or iris structure within 30 days of enrollment or during the study (refer to the relevant attachment of the study reference manual)
10. Subjects who have current or previous usage of an alpha-1-selective adrenoceptor blocking agent or an antagonist of alpha 1A adrenoceptor (e.g., Flomax® (tamsulosin HCl), Terazosin, or Cardura).
11. Subjects who have a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, iridocyclitis, or rubeosis iridis) in either eye.
12. Subjects who have a visual disorder, other than cataracts, that could potentially cause future acuity losses to a level of 20/100 or worse in either eye.
13. Subjects who have had previous intraocular or corneal surgery in either eye, with the exception of laser trabeculoplasty.
14. Subjects with any active preoperative infectious conjunctivitis, keratitis, or uveitis in either eye.
15. Subjects who have a preoperative corneal astigmatism > 1.0 D in either eye as measured by corneal topography or keratometry, irregular astigmatism, or skewed radial axis (note: corneal incisions intended specifically to reduce astigmatism are not allowed during the study).
16. Subjects who cannot achieve a minimum pharmacologic pupil dilation of 5.0 mm in both eyes.
17. Subjects who may be expected to require a combined or other secondary surgical procedure in either eye.
18. Females of childbearing potential (those who are not surgically sterilized or at least 12 months postmenopausal) are excluded from enrollment in the study if they are nursing, lactating, currently pregnant or plan to become pregnant during the study. Females of childbearing potential must be willing to practice effective contraception for the duration of the study.

19. Subjects with any other serious ocular pathology or underlying systemic medical condition (e.g., uncontrolled diabetes) or circumstance that, based on the Investigator's judgment, poses a concern for the subjects' safety or could confound the results of the study.
20. Subjects with abnormal pupillary dilation dynamics (as determined by the medical judgment of the investigator) or eccentric or ectopic pupils in either eye.

Study Materials:

Test Article: The enVista® one-piece hydrophobic acrylic trifocal (MX60EFH) is manufactured by Bausch & Lomb (Clearwater, FL) and is an apodized, diffractive, aspheric biconvex, one-piece intraocular lens (IOL) with a 360° square posterior edge that is a trifocal version of the enVista® MX60E one-piece hydrophobic acrylic IOL with modified C-loop haptics, -0.15 µm spherical aberration. The biconvex lens optic has a body diameter of 6.0 mm, and the overall length (diameter) of the IOL is 12.5 mm. Test lenses will be available in powers +16.0 D to +27.0 D in 0.5 D increments. The study test article will feature axis marks for the assessment of rotational stability in the study. Additional add powers for the enVista trifocal lens are +1.6 D for intermediate vision, +3.1 D for near vision.

Test Article Intended Use: The enVista one-piece hydrophobic acrylic trifocal intraocular lens (IOL) is intended to replace the natural crystalline lens and is indicated for primary implantation for the visual correction of aphakia in adult patients in whom the cataractous lens has been removed (also see **Appendix C**). The lens is intended for placement in the capsular bag.

Control Article: The enVista® one-piece hydrophobic acrylic monofocal IOL (MX60E) is manufactured by Bausch & Lomb (Clearwater, FL) and is an aspheric optic one-piece lens with a 360° square posterior edge. The biconvex lens optic has a body diameter of 6.0 mm, and the overall length (diameter) of the IOL is 12.5 mm. Control lenses will be available in powers +16.0 D to +27.0 D in 0.5 D increments.

Duration of Treatment: Eligible subjects who are enrolled in the study will be followed up to Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).

Clinical Parameters:

- Slit lamp examination
- Visual acuity
- Refractive status
- Intraocular pressure
- Pupil size
- Keratometry
- Corneal topography
- Lens stability (decentration and tilt)
- Patient Reported Outcomes [Quality of Vision (QoV) Questionnaire and Near Activity Visual Questionnaire (NAVQ)]
- Fundus visualization
- Incidence of posterior capsulotomy
- Adverse events
- Defocus curves

- Contrast sensitivity
- Lens rotational stability

The above evaluations, if required by the ISO standard, will be performed as described in ISO 11979-7:2018 [1] unless otherwise specified in the protocol. All other evaluations are described herein.

Study Safety and Performance Variables:

Inherent to the description and analyses of primary study variables is an assumption that adverse events, including serious adverse events and secondary surgical interventions, and changes in visual acuity are independent events for the eyes of each enrolled subject.

Primary Safety Variables:

- The incidence of all serious adverse events, including secondary surgical interventions (SSIs) related to the optical properties of the IOL, through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- The cumulative rate of secondary surgical interventions due to the optical properties of the lens, through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- The incidence of adverse events, through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation), compared to ISO Safety and Performance Endpoint (SPE) rates as defined in ISO 11979-7:2018 Annex E

Secondary Safety Variables:

(Data for these safety variables will be summarized with descriptive statistics lacking hypothesis)

- The incidence of subjects experiencing at least one severe visual disturbance, defined as the highest grade of severity or bothersomeness (separately) reported by subjects using the Quality of Vision (QoV) questionnaire through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Photopic contrast sensitivity with glare at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Mesopic contrast sensitivity with glare at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Mesopic contrast sensitivity without glare at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)

Primary Performance Variables:

- Photopic uncorrected distance visual acuity (UDVA) for first implanted eyes at 4 m at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Photopic uncorrected near visual acuity (UNVA) for first implanted eyes at 40 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Photopic uncorrected intermediate visual acuity (UIVA) for first implanted eyes at 66 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)

Secondary Performance Variables:

- IOL rotation for all trifocal IOL eyes at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Change from baseline (preoperative) in uncorrected photopic near visual acuity (UNVA) at 40 cm for first implanted eyes to Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Change from baseline (preoperative) in uncorrected photopic intermediate visual acuity (UIVA) at 66 cm for first implanted eyes to Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)

Supportive Performance Variables:

(Data for these performance variables will be summarized by treatment group with descriptive statistics lacking hypotheses)

- Photopic corrected visual acuity (CDVA, DCNVA, and DCIVA) for first implanted eyes at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Photopic and mesopic binocular uncorrected near and intermediate visual acuity (UNVA and UIVA) at 40 cm and 66 cm, respectively, at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Binocular CDVA defocus curves from +1.50 D to -3.50 D

Statistical methods:

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Summaries for discrete (categorical) variables will include the tabulation of frequencies and percentages.

Primary Safety Analyses

The proportion of all implanted Safety Set eyes with at least one serious adverse event will be summarized using categorical summary statistics by treatment received. Each eye will be counted only once in the calculation of the rate.

Secondary surgical interventions related to the optical properties of the IOL will be summarized categorically by treatment received for all Safety Set eyes.

Adverse events in all Safety Set eyes will be compared to the ISO Safety and Performance (SPE) threshold rates as described in ISO 11979-7:2018 Annex E.

Secondary Safety Analyses

The incidence of subjects experiencing at least one severe visual disturbance, defined as the highest grade of severity or bothersomeness (separately) reported by subjects using the Quality of Vision (QoV) questionnaire through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation) will be summarized categorically by treatment received for Safety Set subjects using descriptive statistics lacking hypothesis.

Contrast sensitivity results will be summarized using continuous summary statistics by lighting condition, spatial frequency, treatment group and visit.

Primary Performance Analyses

Photopic monocular logMAR UDVA at Post-Operative Visit 4 will be summarized using continuous summary statistics by treatment group for first eyes of the Per Protocol (PP) Set. Imputation of missing data is not conservative in non-inferiority testing. Therefore, missing data will not be imputed for a UDVA non-inferiority test. The treatment effect (mean Test group IOL visual acuity minus mean Control group IOL visual acuity) in logMAR units will be estimated in addition to a one-sided upper 95% confidence limit. If the upper confidence limit for the treatment effect is less than 0.2 logMAR, then the Test lens will be statistically non-inferior to the Control lens.

Photopic monocular uncorrected near visual acuity (UNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation) will be summarized using continuous summary statistics in logMAR units by treatment assignment for the first implanted eyes of ITT Set Subjects. Missing data will be imputed using the Markov chain Monte Carlo (MCMC) multiple imputation method. After imputation of missing data, the statistical hypotheses will be tested using two-sided two-sample t-tests by imputation. An overall p-value resulting from the multiple imputation method will be estimated. The treatment effect (mean Test group IOL VA minus mean Control group IOL VA) in logMAR units will be summarized using continuous summary statistics and a two-sided 95% confidence interval. If the p-value from the multiple imputation analysis is less than or equal to 0.05 and the treatment effect is less than zero (i.e., the Test lens mean logMAR VA is superior to the mean for the control), then it will be concluded that the Test IOL is statistically successful (i.e., superior to the Control IOL) in this outcome.

Photopic monocular uncorrected intermediate visual acuity (UIVA) at 66 cm in first implanted eyes will be summarized and analyzed using the methods described for UNVA.

Secondary Performance Analysis

There is no statistical hypothesis for IOL rotational stability. Trifocal IOL rotation will be judged by criteria contained in ISO 11979-7:2018 Section 6.2.2. The proportion of implanted trifocal IOLs that rotate less than or equal to ten (10) degrees and the proportion of implanted trifocal IOLs rotate less than or equal to twenty (20) degrees between the meridian intended on the day of surgery (Visit 00A/00B) and the meridian observed at Visit 4 will be summarized categorically with descriptive statistics.

If at least 90% of the implanted IOLs rotate less than or equal to ten (10) degrees and at least 95% rotate less than or equal to twenty (20) degrees between the meridian intended on the day of surgery (Visit 00A/00B) and the meridian observed at Visit 4, then the IOL will have demonstrated adequate rotational stability.

Change from baseline treatment effect (mean baseline visual acuity – mean Visit 4 visual acuity) for photopic monocular uncorrected near visual acuity (UNVA) at 40 cm at Post-Operative Visit 4 will be summarized for first eyes of the Test group using continuous summary statistics. A paired t-test will be used to determine if change from baseline is statistically significantly different from zero.

Change from baseline treatment effect (mean baseline visual acuity – mean Visit 4 visual acuity) for photopic monocular uncorrected near visual acuity (UIVA) at 66 cm at Post-Operative Visit 4 will be summarized and analyzed as described for change from baseline in UNVA.
Sample size calculations: Each primary performance endpoint has a statistical power greater than 99% with the planned sample size. Approximately 200 Test group eyes (100 subjects) and 100 Control group eyes (50 subjects) are expected to complete the study. To allow for losses of up to 10%, approximately 224 Test group eyes (112 subjects) and approximately 112 Control group eyes (56 subjects) will be enrolled, or a total of 168 subjects implanted bilaterally (336 eyes).

3 Table of Contents

List of Appendices

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List of Abbreviations and Definitions of Terms

Abbreviation or specialist term	Definition or Explanation
ADE	Adverse Device Effect
AE	Adverse Event
ANSI	American National Standards Institute
C	Centigrade
cd/m^2	Candela per Square Meter
CDVA	Corrected Distance Visual Acuity
CME	Cystoid Macular Edema
cpd	Cycles Per Degree
CRF	Case Report Form
CRO	Clinical Research Organization
D	Diopter
DCIVA	Distance-corrected Intermediate Visual Acuity
DCNVA	Distance-corrected Near Visual Acuity
DRA	Design risk analysis
ETDRS	Early Treatment Diabetic Retinopathy Study
DFU	Directions for Use
F	Fahrenheit
FDA	Food and Drug Administration
FDF	Financial Disclosure Form
GCPs	Good Clinical Practices
ICF	Informed Consent Form
IOL	Intraocular Lens
IOP	Intraocular Pressure
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intent to Treat
logMAR	Logarithm of the Minimum Angle of Resolution
MIOL	Multifocal Intraocular Lens
MTF	Modulation Transfer Function
NAVQ	Near Activity Visual Questionnaire
Nd:YAG	Neodymium:Yttrium Aluminum Garnet
ND	Not Done
OVD	Ophthalmic Viscoelastic Device
PRO	Patient Reported Outcome
PAM	Potential Acuity Meter
PCO	Posterior Capsular Opacification
PP	Per Protocol
QoV	Quality of Vision

Abbreviation or specialist term	Definition or Explanation
SADE	Serious adverse device effect
SAE	Serious Adverse Event
SPK	Superficial Punctate Keratitis
SOP	Standard Operating Procedure
SPE	Safety and Performance Endpoint
SSI	Secondary Surgical Intervention
SUN	Standardization of Uveitis Nomenclature
TASS	Toxic Anterior Segment Syndrome
UDVA	Uncorrected Distance Visual Acuity
UIVA	Uncorrected Intermediate Visual Acuity
UNVA	Uncorrected Near Visual Acuity
VA	Visual Acuity

4 Introduction

Cataracts are a common condition in adults over 40 years of age, and surgical replacement of the cataractous lens with an intraocular lens (IOL) remains an effective way to restore vision to cataract patients. [2] Monofocal IOLs provide adequate distance vision but require spectacle use for near or intermediate distance vision activities. Subsequent to monofocal IOL development and commercialization, multifocal intraocular lenses (MIOLs), including bifocal and trifocal IOLs, have been successfully developed to improve near and intermediate distance vision and increase spectacle independence compared to monofocal IOLs following cataract surgery. [3-7]

There are currently several trifocal IOLs approved in Canada, addressing a desire by cataract surgery patients for a product that provides improved near and intermediate vision in comparison to a conventional monofocal IOL without compromising distance vision. Clinical studies have shown that intermediate add power trifocal diffractive IOLs have substantially improved intermediate vision compared to bifocal IOLs, resulting in better visual quality and excellent spectacle independence for individuals with active lifestyles. [8-12] Observational clinical studies and clinical studies comparing trifocal to bifocal IOLs also have shown high patient satisfaction in patients with trifocal MIOLs. [9, 13, 14] These studies and others indicate contrast sensitivity and levels of photic phenomena in patients with trifocal MIOL implants are similar to that of patients with bifocal MIOLs under both photopic and mesopic conditions, and spectacle independence in up to 100% of the patients has been reported. [10-17]

The enVista® MX60EFH trifocal IOL is a 1-piece hydrophobic acrylic ultraviolet-absorbing intraocular lens intended to replace the natural crystalline lens in adult patients in whom the cataractous lens has been removed. The MX60EFH trifocal IOL is designed with aspheric biconvex optics, designed to have -0.15 µm of spherical aberration, with apodized diffractive structures on the anterior surface, and with a square edge on the posterior surface and modified C-loop haptics. The design and material of the lens allow it to be folded and inserted into the capsular bag through a small incision to minimize the possibility of surgically induced astigmatism. The MX60EFH lens is a modification to the Bausch & Lomb enVista® 1-piece hydrophobic acrylic monofocal IOL, model MX60E, approved under PMA Supplement P920056/S024 by the FDA on 05/23/2017 as an update to PMA P910056/S010, approved on 05/30/2012 for the parent enVista MX60 monofocal IOL. PMA P910056/S010 approved a material change and design modifications to the previously approved Bausch & Lomb model C31UB IOL, including a design change from 3-piece to 1-piece design and the addition of aspheric optics with zero spherical aberration.

The enVista® Trifocal Model MX60EFH will be manufactured, packaged and sterilized with the same materials and processes used for the enhanced enVista® IOL Model MX60E. The enVista Model MX60E lens material is a modification to the enVista Model MX60 material, designed to enhance the unfolding rate of the lens at the lower eye temperature encountered during surgical procedures.

The -0.15 µm negative spherical aberration MX60EFH trifocal IOL lens design (incorporated on the enVista MX60E base refractive design of the posterior surface to give a residual spherical aberration on the average eye of ~0.10µm) is expected to produce comparable decentration performance to a spherical aberration-free lens design and best contrast-related performance in the presence of other higher order aberrations. Mathematical modeling and

optical bench experiments have shown that increased depth of focus due to residual spherical aberration comes at the cost of lower modulation transfer function (MTF). [18] Since the enVista® MX60EFH lens is distance dominant under mesopic (low light) conditions, any level of corneal spherical aberration compensation using the MX60EFH trifocal IOL should result in improving the MTF.

5 Study Objectives and Purpose

The objective of the study is to evaluate the safety and performance of the enVista trifocal intraocular lens when implanted in the capsular bag.

5.1 Study Variables

Inherent to the description and analyses of primary study variables is an assumption that adverse events, including serious adverse events and second surgical interventions, and changes in visual acuity are independent events for the eyes of each enrolled subject.

5.1.1 Safety Variables

The primary safety variables will be:

- The incidence of all serious adverse events, including secondary surgical interventions (SSIs) related to the optical properties of the IOL, through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- The cumulative rate of secondary surgical interventions due to the optical properties of the lens, through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- The incidence of adverse events, through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation), compared to ISO Safety and Performance Endpoint (SPE) rates as defined in ISO 11979-7:2018 Annex E

The secondary safety variables will be:

(Data for these safety variables will be summarized with descriptive statistics lacking hypothesis)

- The incidence of subjects experiencing at least one severe visual disturbance, defined as the highest grade of severity or bothersomeness (separately) reported by subjects using the Quality of Vision (QoV) questionnaire through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Photopic contrast sensitivity with glare at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Mesopic contrast sensitivity with glare at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Mesopic contrast sensitivity without glare at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)

5.1.2 Performance Variables

The primary performance variables will be:

- Photopic uncorrected distance visual acuity (UDVA) for first implanted eyes at 4 m at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Photopic uncorrected near visual acuity (UNVA) for first implanted eyes at 40 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Photopic uncorrected intermediate visual acuity (UIVA) for first implanted eyes at 66 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)

The secondary performance variables will be:

- IOL rotation for all trifocal eyes at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Change from baseline (preoperative) in uncorrected photopic near visual acuity (UNVA) at 40 cm for first implanted eyes to Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Change from baseline (preoperative) in uncorrected photopic intermediate visual acuity (UIVA) at 66 cm for first implanted eyes to Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)

The supportive performance variables will be:(Data for these performance variables will be summarized by treatment group with descriptive statistics lacking hypotheses)

- Photopic corrected visual acuity (CDVA, DCNVA, and DCIVA) for first implanted eyes at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- Photopic and mesopic binocular uncorrected near and intermediate visual acuity (UNVA and UIVA) at 40 cm and 66 cm, respectively, at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation
- Binocular CDVA defocus curves from +1.50 D to -3.50 D

5.2 Overall Study Design and Plan: Description

This will be a prospective, multicenter, randomized, masked, controlled, parallel groups, binocular study at up to approximately twelve (12) clinical sites in Canada with 168 subjects undergoing bilateral cataract extraction and IOL implantation of the enVista one-piece hydrophobic acrylic trifocal IOL (model MX60EFH) or the enVista one-piece hydrophobic acrylic monofocal intraocular lens (model MX60E). The enVista MX60E monofocal IOL was selected as the comparator IOL for this study to confirm or refute the enVista MX60EFH trifocal IOL provides improved near and intermediate visual acuity while maintaining distance visual acuity. The use of a comparator IOL made from the same material assures the results will be independent of the chemical composition of the lenses. Visual acuity improvements are key features of the optical design for the MX60EFH trifocal IOL that should distinguish it from the MX60E monofocal IOL.

Subjects scheduled to undergo cataract surgery by phacoemulsification and bilateral implantation of intraocular lenses (IOLs) will be screened for eligibility. Subjects will be

examined preoperatively to obtain a medical history, establish a baseline for ocular condition, and determine eligibility. Both eyes of each subject will be included in the study and must meet eligibility criteria at the Pre-Operative Visit. At the time of determination of eligibility to participate in the study at the Preoperative Visit, subjects will be successively enrolled at a clinical site and randomly assigned by an interactive response technology (IRT) system in a 2:1 ratio to either the enVista MX60EFH trifocal IOL or the enVista MX60E monofocal IOL, respectively. Randomization information will be obtained only by the Investigator or clinic staff not involved in conducting any post-surgical assessment that requires masking. All staff privy to the randomization assignment will sign attesting their commitment to not share randomization information with anyone other than the Investigator.

Postoperatively, subjects will undergo ophthalmic examinations at regular intervals per the study visit schedule. The Investigator or his/her qualified designee will provide standardized pre-, peri-, and postoperative care for all study subjects at his/her clinical site (refer to **Section 9** for additional information). A delegated examiner(s) at each site who is masked to the randomized assignment of each subject will perform postoperative visual acuity testing. Every effort will be made to ensure that postoperative assessments for a subject are completed by the same examiner.

5.3 Investigators

The clinical investigation will be conducted at up to approximately twelve (12) investigative sites in Canada.

The clinical investigation will be conducted by Investigators who are determined by the Sponsor to be suitably qualified by medical and clinical training and experience as a licensed ophthalmologist to conduct this study in compliance with all applicable Health Canada (HC) regulations, ISO 14155:2020, and local regulations. In particular, Investigators should be familiar with the risks and benefits described in **Section 10.3** and potential adverse events and adverse device effects that may occur, including and not limited to those described in **Section 10.4.1**. Investigator training and experience will be determined by the Sponsor to be suitable based on the Investigator's medical training and licensure.

Each investigative site will attempt to enroll a minimum of approximately ten to fifteen (10-15) subjects. In the event that selected sites do not meet expected enrollment, the Sponsor may decide to increase enrollment as needed at other currently active sites, and/or replace low enrolling or non-enrolling sites, to satisfy study enrollment requirements. No Investigator shall contribute more than 25% of the total subjects in the investigation as specified in ISO 11979-7:2018.Study

5.4 Study Duration

Eligible subjects who are enrolled in this study will be followed to Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).

6 Selection and Withdrawal of Subjects

Approximately one hundred sixty-eight (168) subjects (approximately 336 eyes) at up to approximately twelve (12) clinical sites in Canada scheduled to undergo bilateral

phacoemulsification cataract surgery and IOL implantation of the same assigned IOL will be enrolled in this clinical study.

The study purpose, procedures, and subject responsibilities will be explained to the potential participant. The subject's willingness and ability to meet the follow-up requirements will be determined. When it has been established that the subject is willing to participate, written informed consent will be obtained (*cf.* **Section 0**). To determine eligibility, written informed consent must be obtained from each study subject prior to performing any study specific procedures, those which are not part of the Investigator's routine standard of care. Enrollment will be consecutive enrollment of all eligible subjects. A complete ophthalmic examination will be done at the Preoperative Visit scheduled within 30 days but no less than 5 days before the first eye surgery.

Application of the inclusion and exclusion criteria in the following sections will result in the selection of an investigational population which is approximately representative of the intended target population.

6.1 Subject Inclusion Criteria

This study will include subjects who meet the following inclusion criteria:

1. Subjects must be 18 years of age or older on the date the Informed Consent Form (ICF) is signed.
2. Subjects must have the capability to understand and provide written informed consent on the Institutional Review Board (IRB) / Institutional Ethics Committee (IEC) approved Informed Consent Form (ICF) and authorization as appropriate under local privacy regulations.
3. Subjects must have a clinically significant cataract (cortical, nuclear, subcapsular, or combination) in each eye, as determined by the medical judgment of the Investigator, that is considered amenable to treatment with standard phacoemulsification cataract extraction and capsular IOL implantation, with CDVA equal to or worse than 20/40 in at least one eye, with or without a glare source.
4. Subjects must have a CDVA projected to be equal to or better than 20/32 after IOL implantation in each eye, as determined by the medical judgment of the Investigator or measured by potential acuity meter (PAM) testing, if necessary.
5. Subjects must have clear intraocular media other than the cataract in both eyes.
6. Subjects must have discontinued use of contact lenses for at least 2 weeks (for hard or toric lenses) or 3 days (for soft lenses) prior to the pre-operative examination, and throughout the clinical study.
7. Contact lens wearers must demonstrate a stable refraction (within ±0.50 D for both sphere and cylinder) in both eyes, as determined by manifest refraction on two consecutive examination dates after discontinuation of contact lens wear.
8. Subjects must require an IOL power from +16.0 diopter (D) to +27.0 D in both eyes.

9. Subjects must be willing and able to comply with all treatment and follow-up study visits and procedures, and to undergo second eye surgery within 7-30 days of the first eye surgery.

6.2 Subject Exclusion Criteria

This study will exclude subjects (or eyes) who meet any of the following exclusion criteria:

1. Subjects who have used an investigational drug or device within 30 days prior to entry into this study and/or will participate in another investigation during the period of study participation.
2. Subjects who have any corneal pathology (e.g., significant scarring, guttata, inflammation, edema, dystrophy, etc.) in either eye.
3. Subjects who have significant anterior segment pathology that might increase intraoperative risk or compromise IOL stability (e.g., pseudoexfoliation syndrome, synechiae, iris atrophy, traumatic cataract, lens subluxation, traumatic zonulolysis, zonular dialysis, evident zonular weakness or dehiscence, hypermature or brunescent cataract, etc.) in either eye.
4. Subjects who have uncontrolled glaucoma in either eye.
5. Subjects who have previous retinal detachment or clinically significant retinal pathology involving the macula in either eye.
6. Subjects who have proliferative or non-proliferative diabetic retinopathy in either eye.
7. Subjects who have a congenital ocular anomaly (e.g., aniridia, congenital cataract) in either eye.
8. Subjects with instability of keratometry or biometry measurements.
9. Subjects using any systemic or topical drug known to interfere with visual performance, pupil dilation, or iris structure within 30 days of enrollment or during the study (refer to the relevant attachment of the study reference manual).
10. Subjects who have current or previous usage of an alpha-1-selective adrenoceptor blocking agent or an antagonist of alpha 1A adrenoceptor (e.g., Flomax® (tamsulosin HCl), Terazosin, or Cardura).
11. Subjects who have a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, iridocyclitis, or rubeosis iridis) in either eye.
12. Subjects who have a visual disorder, other than cataracts, that could potentially cause future acuity losses to a level of 20/100 or worse in either eye.
13. Subjects who have had previous intraocular or corneal surgery in either eye, with the exception of laser trabeculoplasty.
14. Subjects with any active preoperative infectious conjunctivitis, keratitis, or uveitis in either eye**.**
15. Subjects who have a preoperative corneal astigmatism > 1.0 D in either eye as measured by corneal topography or keratometry, irregular astigmatism, or skewed radial axis (note: corneal incisions intended specifically to reduce astigmatism are not allowed during the study).
16. Subjects who cannot achieve a minimum pharmacologic pupil dilation of 5.0 mm in both eyes.

17. Subjects who may be expected to require a combined or other secondary surgical procedure in either eye.
18. Females of childbearing potential (those who are not surgically sterilized or at least 12 months postmenopausal) are excluded from enrollment in the study if they are nursing, lactating, currently pregnant or plan to become pregnant during the study. Females of childbearing potential must be willing to practice effective contraception for the duration of the study.
19. Subjects with any other serious ocular pathology or underlying systemic medical condition (e.g., uncontrolled diabetes) or circumstance that, based on the Investigator's judgment, poses a concern for the subjects' safety or could confound the results of the study.
20. Subjects with abnormal pupillary dilation dynamics (as determined by the medical judgment of the investigator) or eccentric or ectopic pupils in either eye.

6.3 Subject Disposition Criteria

6.3.1 Subject Enrollment

The subject is considered enrolled in the study at the time of randomization at the Preoperative Visit and following confirmation on eligibility according to inclusion/exclusion criteria at the Preoperative Visit and again at Visit 00A (Day 0). Randomization should follow the determination the subject has met all inclusion criteria and none of the exclusion criteria.

6.3.2 Subject Screen Failures

A subject who fails to meet eligibility criteria or discontinues from the study of their own volition at the only or last pre-operative screening visit before randomization will be considered a screen failure. Subjects will be seen more than once at a screening visit prior to randomization if they are contact lens wearers to ensure they are adhering to inclusion criteria #6 and #7 and have a stable refraction as described in Appendix B, Section 1.1. Subjects (including contact lens wearers) who do not demonstrate a stable refraction prior to randomization will be screen failed and their data will not be entered in the study database.

6.3.3 Subject Completion

The subject has completed the study when he/she completes Postoperative Visit 4 (Day 120 to Day 180 after second eye IOL implantation). A subject who has missed visits or is missing study measurements will remain in the study. Subjects who require further follow-up for an adverse event (AE) or adverse device effect (ADE) will be followed according to **Section 10.4.5**. The same standard of care will be available for subjects who complete the study as for discontinued subjects (see **Section 6.3.4**) if such additional care is necessary because of the subjects' participation in the clinical investigation and where it differs from that normally expected for the medical condition in question.

6.3.4 Subject Discontinuation

A subject may be discontinued prior to the final study visit for any of the following reasons, including but not limited to:

- Investigator's request (e.g., subject non-compliance or medical decision)

- voluntary withdrawal (subject's request)
- death
- lost to follow-up
- study terminated by Sponsor

A subject may also be discontinued during the first cataract surgery who, during the cataract extraction, experience an anterior or posterior capsule tear or rupture, zonular dialysis, significant iris trauma, or other complication that may cause untoward effects in the judgment of the Investigator. Further, a subject may be discontinued during the first cataract surgery who have zonular instability, need for iris manipulation, or capsular fibrosis or other opacity, or inability to have the IOL fixated in the desired position. In such cases, the subject shall be followed until the condition has stabilized.

Prior to discontinuing a subject, every effort should be made to contact the subject, schedule a final study visit, and obtain as much follow-up data as possible. If a final study visit can be successfully scheduled, the procedures to be completed at that visit are the same as those for Form 4 (Day 120 to Day 180 after second eye IOL implantation) with the exception of procedures for defocus curve and contrast sensitivity sub-studies. Adverse events will be followed as described in **Section 10.4.5**. Subject withdrawals will be documented clearly on the source document and applicable Case Report Forms (CRFs), elements of an electronic data capture (EDC) system.

Notification of subject withdrawals will be made immediately to the Sponsor.

Only subjects who are randomized but did not have the lens inserted into the eye at the first cataract surgery (Visit 00A) may be replaced. Subjects for whom the lens was inserted but not implanted will not be replaced. Subjects who successfully complete Visit 00A and do not successfully implant the assigned IOL at Visit 00B will continue participation for purposes of collecting safety information only for the "B" eye. Visual acuity measurements for a subject who does not implant the assigned IOL at Visit 00B will be only monocular for the "A" eye. A new subject number will be assigned for subject replacements, as long as the total number of treated subjects at the site does not exceed the maximum number specified in **Section 5.3**. Subjects who are discontinued from the study following treatment will not be replaced.

Discontinued subjects and discontinued subject eyes should be followed outside of the study protocol according to the Investigator's normal standard of care.

6.3.5 Lost to Follow-Up

Subjects who do not return for scheduled Postoperative Visit(s), as defined by the visit window, and cannot be contacted, may be considered lost to follow-up. The investigator will try at least twice to reach the subject by telephone and/or electronic mail and will send a follow-up letter by certified mail before considering the subject lost to follow-up. These actions will be recorded in the source documents and a copy of the follow-up letter maintained in the investigator's file. The date of discontinuation for subjects lost to follow-up will be seven days after the date that the unanswered certified letter was sent.

Efforts shall be made to keep the number of subjects lost to follow-up to a minimum, below 10% of the number of subjects randomized.

7 Treatment Plan

7.1 Methods of Assigning Subjects to Treatment Groups

Approximately 168 subjects (336 eyes) will be randomized in a 2:1 ratio to receive the enVista MX60EFH trifocal (Test) IOL or enVista MX60E monofocal (Control) IOL, respectively, in both eyes.

7.1.1 Treatment Allocation

At the time of the Preoperative Visit, subjects will be randomly assigned to either the enVista MX60EFH trifocal IOL or enVista MX60E monofocal IOL in a 2:1 ratio, respectively, based upon a predetermined randomization scheme.

7.1.2 Randomization Method

Subjects will be randomly assigned to receive either the enVista trifocal (Test) IOL bilaterally or the enVista monofocal (Control) IOL bilaterally according to the randomization scheme to be provided.

The IRT system will be utilized for randomization in this study. Randomization will occur following determination of eligibility at the Preoperative Visit, and randomization will be stratified by site such that the ratio of subjects assigned to the Test MX60EFH trifocal IOL or Control MX60E enVista monofocal IOL at each site will be approximately 2:1.

7.1.3 Treatment or Subject Replacement

There is no treatment or subject replacement planned for this study other than that described in **Section 6.3.4**.

7.2 Masking/Unmasking

The Investigator implanting the IOL and designated site personnel will be unmasked to the assignment of IOLs. Subjects and designated postoperative evaluator(s) will be masked to the IOLs assigned. Upon completion of study participation, subjects will be notified of the lens identification that they have received.

A qualified masked examiner at each site, who is unaware of which IOL has been implanted for each subject, shall perform post-operative measurements including manifest refraction, visual acuity, contrast sensitivity, and defocus curves. Every attempt should be made to have the same masked examiner perform the same post-operative measurements for an individual subject throughout the subject's study participation.

In an emergency situation where knowledge of the study treatment is critical to subject safety or the study is prematurely terminated, the study treatment for a subject can be unmasked by the unmasked Investigator. Under normal circumstances, masking should not be broken. The Investigator must record the date, time, and reason for unmasking the study treatment in the source documentation. Individual unmasking by the Investigator will normally result in withdrawal of a subject from the study.

7.3 Concomitant Medications

Documentation of all medications used by the subject within 30 days of informed consent and during the study will be made in study source documents.

Pre-, intra-, and postoperative medications may be administered per the Investigator's standard of care. A complete list of the Investigator's standard regimen of these medications will be provided to the Sponsor or its designee and approved by the Medical Monitor prior to initiation of the study. All Investigators will be required to use Amvisc® Plus viscoelastic as the primary viscoelastic (see **Appendix C** for surgical procedure requirements). A secondary viscoelastic may be used by the Investigator during either cataract surgery at his/her discretion.

Medications known to interfere with visual performance, pupil dilation, or iris structure (except for medications necessary for study procedures) are prohibited within 30 days of enrollment and for the duration of the study. Current or previous usage of an alpha-1-selective adrenoceptor blocking agent or an antagonist of alpha 1A adrenoceptor (e.g., Flomax® (tamsulosin HCl), Terazosin, or Cardura) at any time is also disallowed.

7.4 Protocol Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/IEC and agreed to by the Investigator.

The investigator or designee must document and explain in the subjects' source documentation any deviation from the approved protocol. Protocol waivers will not be allowed under any circumstances, and the Investigators are required to comply with all aspects of the investigational plan. However, the investigator may implement a deviation from, or a change of, the protocol in an emergency situation to protect the rights, safety and well-being of subjects and to eliminate an immediate hazard to study subjects without prior IRB/IEC or Sponsor approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB/IEC for review and approval, to the Sponsor, and to the regulatory authorities, if required.

The date of, and reason for, deviations in all cases will be documented. Protocol deviations affecting the safety of the subject or the integrity of the study must be reported by the Investigator to the IRB/IEC promptly. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB/IEC.

Protocol assessments will continue for a subject until the end of the study, unless the protocol deviation puts the subject at risk or the subject's condition requires that he/she be discontinued from the study.

8 Study Materials and Management

To maintain product integrity and sterility, the investigational devices will be used according to the device instructions and as supplied in their original pouch and outer packaging. At each site, the investigational device will be dispensed by an appropriately qualified member of the study staff assigned by the Investigator to this task.

8.1 Description of Test Article and Intended Use

The enVista MX60EFH Trifocal IOL is manufactured by Bausch & Lomb (Clearwater, FL) and is a one-piece hydrophobic acrylic ultraviolet-absorbing lens with aspheric biconvex optics designed to have -0.15 µm of spherical aberration, with apodized diffractive structures on the anterior surface and modified C-loop haptics, and with intermediate add power of 1.6 D and near add power of 3.1 D. The posterior aspheric optic is designed with a 360-degree square edge, to help prevent Posterior Capsular Opacification (PCO), and modified C-loop haptics. The design and material of the lens allow it to be folded and inserted into the capsular bag through a small incision to minimize the extent of surgically induced astigmatism. Test lenses will be available in powers that are within the range of +16.0 D to +27.0 D, in 0.5 D increments.

The enVista one-piece hydrophobic acrylic trifocal intraocular lens (IOL) is intended to replace the natural crystalline lens in adult patients in whom the cataractous lens has been removed (also see **Appendix C**).

8.1.1 enVista MX60EFH Trifocal IOL Injection Device

The MX60EFH IOL requires the use of the INJ100 or BLIS Bausch & Lomb IOL injection system. INJ100 is a single-use injector system that includes an all-in-one, cartridge, tip & injector unit. The BLIS injector system requires the BLIS-R1 reusable handpiece with the disposable BLIS-X1 cartridge. Investigators who do not have experience with the Bausch & Lomb INJ100 or BLIS injector systems will be trained by the Sponsor or their designee prior to enrolling subjects.

8.2 Description of Control

The enVista One-Piece Hydrophobic Acrylic IOL (Model MX60E) is manufactured by Bausch & Lomb (Clearwater, FL) and is a one-piece foldable, hydrophobic acrylic, ultraviolet (UV) absorbing posterior chamber IOL with an aspheric optic and a 360-degree square edge, to help prevent PCO. The biconvex lens optic has a body diameter of 6.0 mm, and the overall length (diameter) of the IOL is 12.5 mm. Control Model MX60E lenses will be available in powers +16.0 D to +27.0 D, in 0.5 D increments.

8.2.1 enVista MX60E monofocal IOL Injection Device

The enVista MX60E monofocal IOL requires the same injection device as the enVista MX60EFH trifocal IOL.

8.3 Packaging and Labeling

The study materials will be packaged and labeled in a manner consistent with the study design and according to applicable requirements and standards for investigational medical devices.

8.3.1 Packaging

EnVista trifocal MX60EFH and enVista monofocal MX60E lenses will be non-pyrogenic, packaged sterile in 0.9% saline solution, and contained in a gamma grade polypropylene vial

(with a heat-sealed foil lid) that is sealed in a Tyvek peel pouch. The lens is sterilized using gamma irradiation.

8.3.2 Labeling

Each study lens will bear a Bausch & Lomb study label that meets applicable laws for an investigational medical device, which includes, but is not limited to the following information:

- Study number
- Sponsor name and address
- Quantity of contents
- Refer to Directions for Use (DFU)
- Statement indicating: "Exclusively for Clinical Investigations."
- Statement indicating: "To Be Used by Qualified Investigators Only"
- Statement indicating: "Instrument de Recherche"
- Statement indicating: "Réservé uniquement à l'usage de chercheurs compétents"
- Storage conditions
- Device ID number
- Batch number

8.4 Storage of Study Device

Store study IOLs at room temperature. Do not store study IOLs at a temperature greater than 43°C (110°F). DO NOT FREEZE. Do not autoclave the IOLs. Storage should be in a secure location.

8.5 Directions for Use

Refer to **Appendix C** for directions for use during surgery with the MX60EFH and MX60E IOLs.

8.6 Study Device Accountability

The Investigator will be responsible for keeping current and accurate records of the number of IOLs received, implanted and returned to Sponsor on the IOL Treatment/Accountability Log. The IOLs must be stored under the appropriate conditions in a secure area and are to be implanted only in subjects enrolled in the study, in accordance with the conditions specified in this protocol. During the course of the study, the Investigator must maintain an inventory of all investigational IOLs implanted, including subject identifiers.

Accountability records will include:

- The lens numbers of all IOLs received, the receipt date, and the quantity received
- The names of all site personnel who received, used, or disposed of the IOLs
- The dates of use, disposal, or return of each IOL
- A record of each subject implanted with a Test or Control IOL
- Number of IOLs returned to the Sponsor
- Explanation for reconciliation of discrepancies

At various time points throughout the study and/or upon completion of the study, the Sponsor or Sponsor's representative will review and verify the Investigator's accountability records (refer to the relevant attachments of the study reference manual).

8.7 Device Returns/Destruction

Following verification, and as directed by the Sponsor, unused study devices must be returned to the Sponsor. Study devices should not to be destroyed by site unless returning the device to the Sponsor is not a viable option. All device returns will be listed on the Investigational IOL Return Form and returned with devices. The Sponsor will be responsible for complete study accountability, returns, reconciliation and destruction of the returned IOLs at the conclusion of the study.

8.8 Other Materials

Study materials provided by Bausch & Lomb will include:

- Bausch & Lomb single-use IOL injection system (BLIS)
- Bausch & Lomb IOL injector Model INJ100
- Bausch & Lomb Amvisc® Plus viscoelastic
- Visual acuity and contrast sensitivity instrumentation (calibrated according to the manufacturer's specifications)
- Patient reported outcome questionnaires, the Quality of Vision (QoV) questionnaire[21, 22] and the Near Activity Visual Questionnaire [23-26]
- Accessory to enable capture of slit-lamp biomicroscope photos, as needed
- Pupillometer, as needed (calibrated according to the manufacturer's specifications, if required)

9 Study Procedures and Evaluations

Subjects will be examined and evaluated according to the study schedule provided in **Appendix A.**

9.1 Schedule of Evaluations and Procedures

Enrolled subjects who meet eligibility criteria will be seen according to the following schedule:

Visit Name	Eyes Evaluated	Visit Window
Preoperative Visit 0A/B	Both Eyes	Day -30 to -5
Operative Visit 00A	1st Eye	Day 0
Post-Operative Visit 1A	1st Eye	Day 1 to 2 post Visit 00A
Post-Operative Visit 2A	1st Eye	Day 7 to 14 post Visit 00A
Post-Operative Visit 3A	1st Eye	Day 30 to 60 post Visit 00A
Operative Visit 00B	2nd Eye	Day 7 to 30 post Visit 00A
Post-Operative Visit 1B	2nd Eye	Day 1 to 2 post Visit 00B
Post-Operative Visit 2B	2nd Eye	Day 7 to 14 post Visit 00B

Post-Operative Visit 3B	2nd Eye	Day 30 to 60 post Visit 00B
Post-Operative Visit 4	Both Eyes	Day 120 to Day 180 post Visit 00B

Refer to **Appendix A** for the schedule of visits and procedures and **Appendix B** for methods of clinical evaluation.

Following identification of a potential subject, the Investigator (or designee) will explain the purpose of the study, procedures, risks/benefits, and subject responsibilities to the potential subject. The subject's willingness and ability to meet the follow-up requirements of the study will be determined. If the subject chooses to participate in the investigation, written informed consent will be obtained. The subject and the person obtaining written consent will sign and date the IEC-approved informed consent form (ICF), at which point the subject is considered part of the study population. The original signed document will be retained in the subject records, and a copy will be provided to the subject. In addition, the applicable privacy regulation requirements and standards must be met. Standards for privacy to be followed are described in the ICF.

The subject identification number will be assigned by the IRT system, which will consist of a 3-digit site number (pre-assigned) and a 3-digit chronological order screening number, assigned by the IRT system and starting with 001 (e.g., 101001, 101002; in this example the site number is 101). That subject number will be used to identify the subject throughout the study. It will not be necessary for the surgical procedures to occur in subject number order.

9.1.1 Preoperative Visit 0: Day -30 to Day -5

Informed consent must be obtained prior to the Investigator performing study specific procedures that are not part of his/her routine standard of care. After obtaining written informed consent, prospective subjects will be screened to determine whether they meet the entry criteria for the study. If the subject is eligible for participation after review of the inclusion and exclusion criteria, the subject will undergo further testing as listed in **Appendix A** prior to randomization. If they continue to be eligible, the subject will be enrolled and assigned to a randomized treatment cohort (MX60EFH trifocal IOL or MX60E monofocal IOL). Demographic information, medical history, and current medication use will be collected. The preoperative clinical evaluation will be conducted no more than 30 days prior to the first surgery and will consist of a complete ophthalmic examination.

Note: Potential subjects may be identified for screening in conjunction with routine clinic cataract evaluations involving standard of care testing. To avoid having to repeat this testing within a short time period to qualify for the study, standard of care measurements, including corneal topography, targeted refraction / IOL power calculation / axial length determination / anterior chamber depth / chord length μ, keratometry, IOP, slit-lamp examination, and dilated fundus exam, may be used as qualifying pre-operative assessments, provided they meet the following criteria:

- Performed by a qualified investigator and/or their designee who is participating in the study;
- Performed as specified in the protocol to verify subject eligibility;

- Conducted within the pre-operative window specified in the protocol.

9.1.2 Operative Visit 00A: Day 0

Subjects will be assessed to reconfirm eligibility. In addition, any changes in concomitant medications or AEs will be recorded. If the subject is no longer eligible, he/she will be discontinued from the study. If the subject is eligible, surgery will be performed using the surgical procedure described in **Appendix C**.

The eye with the worse corrected distance visual acuity (CDVA) or worse CDVA with glare at the Preoperative Visit will be treated first (eye A) and used in the performance of monocular evaluations. If CDVA is the same for both eyes, the right eye will be treated first.

9.1.3 Operative Visit 00B: Day 7 to 30

Subjects will undergo the second eye surgery (eye B) between 7 and 30 days from the first eye surgery. Postoperative Visit 2A must be completed before Visit 00B. These visits may be performed the same day at the Investigator's discretion, provided Visit 2A is done first, and both visits are performed within window. If the subject continues to meet eligibility criteria, surgery will be performed using the surgical procedure described in **Appendix C**. If, at the time of the second eye surgery, the "B" eye is deemed ineligible or surgical complications arise that require discontinuation of the "B" eye, a commercially available non-study lens will be implanted in that eye, if possible. The subject will remain in the study and will be followed for the duration of the study with only safety information recorded for the "B" eye at study visits after it is discontinued from the study. Visual acuity measurements for a subject who does not implant the assigned IOL at Visit 00B will be only monocular for the "A" eye.

9.1.4 Postoperative Visits (1A through 4): Day 1 to Day 180

All treated subjects will be seen for seven (7) postoperative visits. Postoperative Visits 3A and 3B may be performed the same day at the Investigator's discretion, provided Visit 3A is done first, and both visits are performed within window. Procedures conducted at these study visits are those listed in **Appendix A**.

9.1.5 Unscheduled Visit(s)

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional examinations should be fully documented in the source documents and on Unscheduled Visit CRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit window are not Unscheduled Visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit CRF.

If a subject is seen for multiple visits during a given visit timeframe, the data from the visit that is intended to meet the protocol requirements for the scheduled visit will be captured on the visit CRF. Where such a determination cannot be made, the first visit within the scheduled visit interval will be used for completion of the protocol required scheduled visit CRF. Data from any additional visits within a scheduled visit interval will be captured on an Unscheduled Visit CRF.

9.1.6 Missed Visit(s)

If a subject misses any scheduled follow-up visit and cannot be seen prior to the start of the visit range for the next scheduled follow-up visit, the visit is considered missed.

9.2 Post-Study Follow-Up

If a subject requires further follow-up upon discontinuation or completion of the study, the Investigator should schedule post-study follow-up visits, as necessary. Refer to **Section 10.4.5** for follow-up of AEs following study exit.

9.3 Study Completion

The Sponsor or its representative will notify the Investigator and/or the IRB/IEC, as applicable, to inform them when the study is complete. The study will be considered complete when all enrolled subjects either have completed study visits through Visit 4 or have been discontinued from the study prior to Visit 4 for any reason.

9.3.1 Early Study Termination

If during the study it becomes evident to the Sponsor that the study should be stopped prematurely, the study will be terminated, and appropriate notification will be given to the Investigator(s), IRB/IEC, and HC and/or local Health Authority, as applicable. The Sponsor or its representative will instruct the Investigators to stop enrolling and dispensing study materials/treatment and to arrange for study closeout at each site as appropriate. Masking of treatment assignments will continue until the Sponsor unmasks the study.

10 Primary and Secondary Safety and Performance Variables

10.1 Evaluation of Safety

The primary safety variables will be:

- The incidence of all serious adverse events, including secondary surgical interventions (SSIs) related to the optical properties of the IOL, through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- The cumulative rate of secondary surgical interventions due to the optical properties of the lens, through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation)
- The incidence of adverse events, through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation), compared to ISO Safety and Performance Endpoint (SPE) rates as defined in ISO 11979-7:2018 Annex E

The secondary safety variables will be:

(Data for these safety variables will be summarized with descriptive statistics lacking hypothesis)

- The incidence of subjects experiencing at least one severe visual disturbance, defined as the highest grade of severity or bothersomeness (separately) reported by subjects

using the Quality of Vision (QoV) questionnaire through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).

- Photopic contrast sensitivity with glare at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).
- Mesopic contrast sensitivity with glare at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).
- Mesopic contrast sensitivity without glare at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).

10.2 Evaluation of Performance

The primary performance variables will be:

- Photopic uncorrected distance visual acuity (UDVA) for first implanted eyes at 4 m at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).
- Photopic uncorrected near visual acuity (UNVA) for first implanted eyes at 40 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).
- Photopic uncorrected intermediate visual acuity (UIVA) for first implanted eyes at 66 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).

Secondary Performance Variables:

- IOL rotation for all trifocal eyes at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).
- Change from baseline (preoperative) in uncorrected photopic near visual acuity (UNVA) at 40 cm for first implanted eyes to Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).
- Change from baseline (preoperative) in uncorrected photopic intermediate visual acuity (UIVA) at 66 cm for first implanted eyes to Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).

The supportive performance variables will be:

(Data for these performance endpoints will be summarized by treatment group with descriptive statistics lacking hypothesis)

- Photopic distance-corrected visual acuity (CDVA, DCNVA, and DCIVA) for first implanted eyes at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).
- Photopic and mesopic binocular uncorrected near and intermediate visual acuity (UNVA and UIVA) at 40 cm and 66 cm, respectively, at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation).
- Binocular CDVA defocus curves from +1.50 D to -3.50 D.

10.3 Risk Assessment, Risk Mitigation, and Anticipated Benefit

The model MX60EFH IOL has similar material, mechanical, and biocompatibility properties to the FDA-approved model MX60 and optically equivalent MX60E monofocal IOLs that have

been shown to be safe for implantation in humans. [27, 28] Reduced contrast sensitivity and increased visual disturbances, such as glare and halo, are known to occur more frequently with multifocal IOLs and will be evaluated in this study through the patient reported outcome (PRO) Quality of Vision questionnaire and a contrast sensitivity sub-study.

The known risks of multifocal IOL implantation that exist in addition to the risks of monofocal IOLs include the following:

- Under scotopic and mesopic conditions, the patient has reduced contrast sensitivity,
- There is an increased risk of post-operative photic effects such as halos and glare.

Studies on other adverse perception effects following multifocal IOL implantation, such as stereo acuity disturbances and aniseikonia, have generally indicated an acceptable performance range. [29]

Multifocal IOLs achieve correction of presbyopia by dividing incoming light into two or more focal points. Patient selection and counselling are particularly important with these IOLs. There may be a symptomatic reduction in the quality of distance vision, particularly if other ocular pathology is present. Therefore, the candidacy of patients with amblyopia or abnormalities of the cornea, optic disc, and macula for a multifocal IOL must be carefully considered. Although uncommon, explantation of multifocal IOLs may become necessary if optical side effects are intolerable. [30]

A Cochrane systematic review concluded that multifocal IOLs are effective at improving near vision relative to monofocal IOLs, although there is uncertainty as to the size of the effect. Whether that improvement outweighs the adverse effects of multifocal IOLs, such as glare and haloes, will vary between people. Motivation to achieve spectacle independence is likely to be a deciding factor. [31]

Mitigation of the risks related to undesirable optical phenomena of multifocal IOLs includes exclusion of potential subjects with ocular pathology which may limit the quality of postoperative vision such as abnormalities of the cornea, lens capsule-zonular apparatus and macula, as well as thorough discussion of the characteristics of dysphotopsia such as halos, glare and reduced contrast sensitivity during the informed consent process. As noted above, candidacy of patients for multifocal IOL implantation depends not only on objective findings during a complete ophthalmologic examination, but also on patients' motivation to achieve spectacle independence. The risks and benefits must be weighed on an individual basis by the investigator in consultation with each potential subject. Ensuring the subject's thorough understanding of the optical side-effects of multifocal IOLs and ascertaining the subject's degree of enthusiasm for spectacle independence form the basis of informed consent and risk mitigation.

Despite concern about risks of multifocal IOL implantation, the value of conducting a clinical study to support approval of a multifocal IOL is substantial in terms of providing another IOL option to increase potential patient satisfaction and improved near and intermediate vision while maintaining good distance vision. Prior studies of multifocal IOLs have shown a high degree of patient satisfaction, both in absolute terms and compared to monofocal IOLs, improved near vision, and a very low rate of IOL explantation due to optical side-effects. [31-34]

These results indicate that application of the principles of informed consent and patient selection to the risk of dysphotopsia and contrast sensitivity reduction will provide greater

benefit than risk and justify the enrollment of subjects in this study of a multifocal IOL. Specifically, we have done a design risk analysis for the enVista MX60EFH trifocal IOL and have concluded no mitigations is needed beyond that stated in the Section.

An anticipated benefit which a subject may derive from participation in this study is an improvement of their vision as a result of the removal of their cataracts. If the subject is randomized to receive the enVista MX60E monofocal IOL, it is expected they will have improvement in their distance vision and would then require the use of corrective lenses (such as glasses or contact lenses) for near and intermediate vision. If a subject is randomized to receive the enVista MX60EFH trifocal IOL, they may have improvement in their near and intermediate vision while maintaining comparable distance visual acuity to a monofocal IOL, allowing them to be able to read, use a computer, and watch television without reading glasses or bifocals.

Further discussion of potential or actual risks during cataract surgery and with the use of multifocal or monofocal enVista IOLs as well as IOL injectors to be used in this study can also be found and should be accessed in the study Investigator's Brochure and/or the relevant IOL Directions for Use (DFU) provided by the Sponsor as manufacturer. Of note, the enVista IOL medical devices according to the Design Risk Analysis (DRA) are not susceptible to environmental influences or concomitant medical treatments once implanted in a patient's eye.

10.4 Adverse Events

Each subject eye treated must be examined for the presence/absence of adverse events at all visits, whether scheduled or not. If an adverse event (AE) occurs, the first concern will be the safety and welfare of the subject; treatment should be provided as appropriate for the event.

10.4.1 Adverse Events Definitions

For the purposes of this study, adverse events include: all ocular AEs; all ocular and non-ocular serious adverse events (SAEs); adverse device effects (ADEs); and serious adverse device effects (SADEs). Non-ocular adverse events other than non-ocular SAEs will not be collected because of their lack of influence on assessing safety of the Test and Control IOLs. AEs, SAEs, ADEs and SADEs are defined as follows.

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory finding) in a subject, user or other persons, whether or not related to the investigational medical device. This definition includes events related to the medical device or procedures involved. For users or other persons, this definition is restricted to events related to the study device.

A Serious Adverse Event (SAE) is an AE that leads to:

- death
- a serious deterioration in the health of the subject that either results in:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or body function (e.g., blindness), or
    - in-patient or prolonged hospitalization, or
    - a potentially vision-threatening condition, or

  - medical or surgical intervention to prevent life- or vision-threatening illness or injury or permanent impairment to a body structure or a body function
- fetal distress, fetal death, or a congenital abnormality or birth defect

Planned hospitalization for a pre-existing condition will not be considered a serious adverse event.

An Adverse Device Effects (ADE) is any adverse event related to the use of an investigational medical device or an approved medical device used as a comparator. This definition includes any events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device. This definition also includes any event resulting from device malfunction, use error, inadequate labeling, or from intentional misuse of the investigational medical device.

A Serious Adverse Device Effect (SADE) is any ADE which also meets any of the serious criteria for SAEs.

Anticipated AEs associated with cataract surgery and/or premium IOL implantation that might reasonably be expected to occur in this study, however rare, are listed below and include, but are not limited to, the following:

Anterior capsule tear
Anterior uveitis (including iritis and iridocyclitis) *
Capsular block syndrome
Choroidal detachment/hemorrhage
Corneal edema *
Cystoid macular edema (CME) *
Difficulty with tasks in dim light resulting in secondary surgical intervention*
Elevated IOP*
Endophthalmitis (intraocular inflammation requiring vitreous tap and use of intraocular antibiotics)
Events resulting in unplanned secondary surgical intervention other than paracentesis to relieve pressure prior to 1 week postoperative or Nd:YAG capsulotomy
Flat anterior chamber
Hyphema
Hypopyon
Incorrect IOL power resulting in secondary surgical intervention *
Increased glare or halos
Infectious keratitis
IOL damage resulting in secondary surgical intervention *
IOL decentration or tilt *
Iris or pupil damage
Loss of BCVA*

Mechanical pupillary block (A shallowing of the peripheral and/or central anterior chamber with or without elevation of IOP by obstruction of the flow of aqueous humor from the posterior chamber through the pupil to the anterior chamber). This may be induced by the crystalline lens, vitreous face, or implanted devices.)

Multiple (or "ghost") images other than increased glare or halos

Pain *****

Posterior capsular rupture

Progression or onset of diabetic retinopathy

Progression or onset of macular degeneration

Reduced contrast sensitivity

Retained lens material

Retinal detachment (partial or complete RD associated with retinal tear)

Secondary IOL intervention (reposition, exchange, or removal) for any reason *

Synechiae formation

Undesirable optical phenomena resulting in secondary surgical intervention

Thermal injury (phaco burn)

Toxic anterior segment syndrome (TASS) (An acute, noninfectious inflammation of the anterior segment of the eye that develops within 24 to 48 hours after surgery and is characterized by corneal edema and accumulation of white cells in the anterior chamber of the eye)

Vitreous prolapse

Wound leak (positive Seidel)

* These events may be considered normal or expected events after cataract surgery and only need to be reported as AEs/SAEs if present as specified below:

- Iritis/cells/flare characterized by grade 1+ cells or greater using SUN criteria[37] if persistent for greater than 3 months after surgery, or relapses in less than 3 months after discontinuation of therapy, or the subject is maintained on therapy for more than 3 months to control inflammation
- Corneal or corneal wound edema resulting in CDVA of ≤20/40 at Visit 3A or later in the first implanted eye or at Visit 3B or later in the second implanted eye, or any persistent corneal or corneal wound edema present at Visit 4
- Cystoid macular edema diagnosed by clinical exam and adjunct testing (eg. OCT, FA or other method), resulting in CDVA of ≤ 20/40 at Visit 3 or later
- Elevation of IOP by ≥10 mmHg above baseline (pre-operative) to a minimum of 25 mmHg after Visit 1A in the first implanted eye or after Visit 1B in the second implanted eye, or elevated IOP requiring treatment if present at Visit 4
- Postoperative refractive error > 1.0 D different from predicted, and not due to calculation or other use error
- Crack, breakage or deformity of IOL haptic or optic resulting in secondary surgical intervention

- IOL decentration or tilt likely to affect visual outcome and resulting in secondary intervention
- Monocular CDVA decrease of equal to or greater than 2 lines (≥10 letters) from any previous visit not secondary to any underlying condition, or any monocular CDVA decrease from any previous visit of greater than 2 lines if persistent to the subject's last visit in the study.
- Pain, per subjective patient reporting, graded as ≥ 4 on the standardized pain rating scale (from 0 to 10)
- Mild superficial punctate keratitis (SPK) present at Visit 3A or later in the first implanted eye or at Visit 3B or later in the second implanted eye, or moderate, severe, or very severe SPK at any post-operative visit (note: if SPK is present pre-operatively, adverse event must be reported only if there is a worsening)

Note: Posterior capsular opacification (PCO) is NOT to be reported as an AE unless the Investigator treats PCO with Nd:YAG laser exposure.

10.4.2 Identification and Collection

Identification and collection of an AE begins after informed consent has been obtained and documented. Standard sources of identifying AEs include:

- direct observation by the Investigator
- asking of the study participant a non-specific question (e.g., "Have you had any problems since the last visit?")
- unsolicited volunteering of information by the study participant (e.g., "Doctor, I have had blurred vision since I started using this lens.")
- laboratory or test results that meet protocol requirements for classification as an AE

Specific to this protocol, ocular AEs in the study eye(s) and all SAEs (ocular and non-ocular) observed or elicited by the Investigator, reported by the subject, or resulting from a test result, etc., occurring during the clinical investigation must be reported in the CRF for randomized subjects. For screen failures, AEs are recorded in the source data only, but not in the CRF. Note: The expedited reporting of SAEs with enrolled subjects as described below also applies for screen failures. During the study, the Investigator should treat the study subject as appropriate to ensure his/her safety and welfare. Refer to **Section 10.4.5** for additional information pertaining to ongoing AEs at subject exit.

Pre-existing conditions will not be considered AEs but will be collected at the Preoperative Visit as medical history. A worsening of a pre-existing condition during the study should be documented as an AE and evaluated accordingly.

Hospitalizations for admission without a medical AE should be captured as a serious AE until the cause of hospitalization can be identified. However, the following reports of hospitalization without a medical AE should not be considered either serious or an AE:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of the pre-existing condition (e.g., for work-up of persistent pretreatment lab abnormality)
- Social admission (e.g., subject has no place to sleep)
- Administrative admission (e.g., for yearly physical exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)

10.4.3 Evaluations

When evaluating AEs, the Investigator must determine if the event is serious or non-serious (refer to **Section 10.4.1** for criteria), assess the severity of symptoms, and determine the relationship of the event to the device, using the following guidelines:

a. Severity

- **Mild**: Subject awareness of a sign or symptom that is easily tolerated, requires no treatment, and does not interfere with subject's daily activities
- **Moderate**: Subject awareness of a sign or symptom which may be a low level of concern to the subject and may interfere with daily activities, but can be relieved by simple therapeutic care
- **Severe**: A sign or symptom that interrupts the subject's daily activity and requires systemic therapy or other treatment

b. Relationship to Study Device or Surgical Procedure

- **Related**: There is at least a reasonable possibility the AE is related to the study device or surgical procedure. Reasonable possibility includes the following causality assessments:
    - Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
    - Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
    - Causal relationship: the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
        - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
        - the event has a temporal relationship with investigational device use/application or procedures;

- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time.

- **Unrelated**: There is little or no reasonable possibility the AE is related to the study device or surgical procedure. No reasonable possibility means there is no evidence to suggest either a causal relationship or association between the study device or surgical procedure and the AE. No reasonable possibility includes the following assessments:
  - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
  - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
  - the event involves a body-site or an organ that cannot be affected by the device or procedure;
  - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
  - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time.

10.4.4 Reporting

10.4.4.1 Actions Required by Investigators

Actions required by Investigators for reporting of adverse events are summarized in **Table 1** and **Table 2** below.

Table 1. Non-serious Ocular Adverse Events

Non-serious ocular AEs	Non-device-related	Device-related
Required Action	Recorded on Adverse Event CRF only; no expedited report to Health Canada, Sponsor, or IRB/IEC	

Table 2. Serious Adverse Events

SAEs	Non-device-related	Device-related (SADE)
Required Action	-Recorded on SAE Report Form and AE CRF. -Investigator submits expedited report to Sponsor and its representative within 48 hours. -Report to IRB/IEC if required per IRB/IEC policy.	-Recorded on SAE Report Form and AE CRF -Investigator submits expedited report to Sponsor and its representative within 48 hours. -Report to IRB/IEC within 10 days, or earlier if required per IRB/IEC policy.

		- Investigator must also submit SADE as a Mandatory Problem Report to HC within 72 hours of discovery.

10.4.4.2 SAE Reporting

The Investigator must report any serious adverse event (related or unrelated) to the Sponsor and its representative in an expedited manner if it meets the criteria for a SAE.

The Investigator must forward the SAE/SADE Report Form and any available supporting documents to the Sponsor or its designee within 48 hours of becoming aware of an event.

The contact for reporting SAEs is:

[redacted]

The contact for reporting SADEs is:

[redacted]

All device related serious adverse events (SADEs) must be reported to the reviewing IRB/IEC within no more than 10 working days following first awareness of the SADE or according to the established reporting timelines of the IRB/IEC, whichever is shorter. If required, the Investigator must also report non-device related serious adverse events (SAEs) to the reviewing IRB/IEC according to the established reporting procedures and timelines. When participating in multicenter clinical investigations, the Investigator also may receive off-site SAE reports. These are reports of SAEs which occurred at other clinical sites for the same trial, or in different trials, but with the same investigational device. The Investigator must forward such reports to IRB/IEC according to the established reporting procedures within 10 days or earlier if required by IRB/IEC. When participating in multicenter clinical investigations,

Principal Investigators also may receive off-site SADE reports. These are reports of SADEs which occurred at other clinical sites for the same trial, or in different trials

10.4.4.3 Mandatory Problem Reporting

The qualified investigator is required to report any Mandatory Problems to Health Canada within 72 hours of discovery. Mandatory Problems are cases in which the incident:

- Is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use.

and

- Has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur. A serious deterioration in health means a life-threatening disease, disorder or abnormal physical state, the permanent impairment of a body function or permanent damage to a body structure, or a condition that necessitates an unexpected medical or surgical intervention to prevent such a disease, disorder or abnormal physical state or permanent impairment or damage. The term "permanent" means irreversible impairment or damage to a body structure or function, and necessarily excludes minor impairment or damage. Medical intervention is not in itself a serious deterioration in health. The reason that motivated the medical intervention should be used to assess the reportability of an incident.

For this protocol, all SADEs will be Mandatory Problems.

The contacts for Mandatory Problem Reporting for Health Canada are as follows:

Email: hc.mdpr-dimm.sc@canada.ca

Or

Fax: 613-954-0941

Any reports which are reported to Health Canada as a Mandatory Problem, must also be submitted to the Sponsor per applicable timelines.

10.4.4.3.1 Mandatory Problem Reporting by Sponsor

A Preliminary Report will be sent to Health Canada, IRB/IEC, and investigators:

- Within 10 days after Sponsor becomes aware of a Mandatory Problem that has led to the death or a serious deterioration in the state of health of a patient, user or other person, or

- Within 30 days after Sponsor becomes aware of a Mandatory Problem, if the Mandatory Problem has not led to the death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur.

A Final Report will be submitted to Health Canada, IRB/IEC, and investigators upon final assessment of the Preliminary Report by the Sponsor.

10.4.4.4 Reporting Device Deficiencies

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

Investigators must evaluate, record, and report via applicable forms any complaints/deficiencies or malfunctions experienced with a Test or Control lens during this trial to the Sponsor and its representative promptly. The Sponsor shall review all device deficiencies, and, upon the Sponsor's request, Investigators must supply any additional information related to the safety reporting of a particular event. Test and Control lenses that are associated with a device deficiency are to be returned to the Sponsor or their representative without delay.

If the device deficiency is associated with or caused an SAE, then the device deficiency meets the criteria of a Mandatory Problem, then the Mandatory Problem Reporting procedure and timelines must be followed as per **Section 10.4.4.3 in addition to device deficiency reporting procedures.**

If no SAE/SADE was associated with or caused by the device deficiency, then the following assessment must also be made for the deficiency:

- Deficiency might have led to an SAE/SADE if suitable action had not been taken or intervention had not been made or if the circumstance had been less fortunate

The contact for reporting device deficiencies is:

[redacted]

10.4.4.4.1 Reporting of Deficiencies for Marketed Products

Any deficiency related to ancillary marketed products used in this study should be reported by the Investigators to the Sponsor or manufacturer according to the marketed product directions for use, and to other parties in accordance with the country and regional requirements.

10.4.5 Adverse Events at Subject Exit

Ongoing AEs will be followed until resolution, no further change in the condition is expected (i.e., event stabilized), or as dictated by standard of care. Documentation in the CRF of this follow-up is not required although subject care should continue as appropriate.

Ongoing SAEs and SADEs will be followed by the Sponsor and its representative(s) and the Investigator until the outcome is determined or until no further change in the condition is expected.

10.4.6 Pregnancy

During the study, all female subjects of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). Female subjects who become pregnant during the study will be followed until completion of pregnancy. Every effort will be made to obtain the health status of the mother and infant or fetus (in cases of miscarriage or therapeutic abortion) at term. Pregnancy itself is not considered an AE.

All confirmed pregnancies must be immediately reported to the medical monitor and CRO contact within 48 hours of the investigator's awareness of the pregnancy. All confirmed pregnancies must be reported via confirmed facsimile or email transmission and must be submitted on a Pregnancy Report form to the Sponsor or designee within 48 hours of the investigator's awareness of the pregnancy.

The contact for reporting pregnancies is:

[redacted]

11 Statistics

11.1 Hypotheses

The purposes of this clinical investigation are to show that the Test lens, when implanted in the capsular bag, is safe and that, compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity while maintaining comparable distance visual acuity.

The critical region for rejection of null hypotheses will be a p-value ≤ 0.05 unless otherwise specified. This applies to one-sided hypotheses as is customary for IOL trials.

11.1.1 Safety Endpoints

11.1.1.1 First Primary Safety Endpoint

The goal of this endpoint is to estimate the proportion of eyes with at least one serious adverse event. There is no statistical hypothesis associated with the proportion of first implanted ITT eyes with at least one serious adverse event through Form 4 (Visit 4, Day 120 to Day 180 after second eye IOL implantation).

11.1.1.2 Second Primary Safety Endpoint

The goal of this endpoint is to estimate the proportion of eyes with at least one secondary surgical intervention due to the optical properties of the lens. The second primary safety endpoint is the rate of secondary surgical interventions due to the optical properties of the lens through Form 4 (Visit 4, Day 120 to Day 180 after second eye IOL implantation). There is no statistical hypothesis associated with this endpoint.

11.1.1.3 Third Primary Safety Endpoint

The goal of this endpoint is to determine whether the rate of any ISO grid AE is inferior to the historical control rate. For each ISO 11979-7:2018 Annex E SPE grid AE, the null and alternative hypotheses are as follows:

$$H_0: \pi \leq \pi_0$$
$$H_1: \pi > \pi_0$$

Where:

- π = the proportion of Test (trifocal) eyes with the adverse event, and
- π_0 = the historical control proportion of eyes with the adverse event given in the ISO 11979-7 SPE grid

11.1.2 Performance Endpoints

11.1.2.1 Primary Performance Endpoints

11.1.2.1.1 First Primary Performance Endpoint: UDVA

The goal of the first primary performance evaluation is to show that the Test lens is noninferior to the Control lens in uncorrected distance visual acuity. For the first primary performance endpoint, mean photopic monocular logMAR UDVA in first implanted eyes at Post-Operative Visit 4, the null (H_0) and alternative (H_1) hypotheses are as follows:

$$H_0: \mu_T - \mu_C \geq 0.2$$
$$H_1: \mu_T - \mu_C < 0.2$$

Where:

- μ_T = the mean logMAR UDVA of the Test (trifocal) group, and
- μ_C = the mean logMAR UDVA of the Control (monofocal) group

11.1.2.1.2 Second Primary Performance Endpoint: UNVA

The goal of the second primary performance evaluation is to show that the Test lens is superior to the Control lens in uncorrected near visual acuity. For the second primary performance endpoint, mean photopic monocular logMAR UNVA in first implanted eyes at Post-Operative Visit 4, the null and alternative hypotheses are as follows:

$$H_0: \mu_T = \mu_C$$
$$H_1: \mu_T \neq \mu_C$$

Where:

- μ_T = the mean logMAR UNVA of the Test (trifocal) group, and
- μ_C = the mean logMAR UNVA of the Control (monofocal) group

11.1.2.1.3 Third Primary Performance Endpoint: UIVA

The goal of the third primary performance evaluation is to show that the Test lens is superior to the Control lens in uncorrected intermediate visual acuity. For the third primary performance endpoint, mean photopic monocular logMAR UIVA in first implanted eyes at Post-Operative Visit 4, the null and alternative hypotheses are as follows:

$$H_0: \mu_T = \mu_C$$
$$H_1: \mu_T \neq \mu_C$$

Where:
μ_T = the mean logMAR UIVA of the Test (trifocal) group, and
$\boldsymbol{\mu_C}$ = the mean logMAR UIVA of the Control (monofocal) group

11.1.2.2 Secondary Performance Endpoints

11.1.2.2.1 Rotational Stability

The goal of this endpoint is to show that the rotational stability of the enVista® Trifocal IOL is acceptable. Trifocal IOL rotational stability will be determined from photographic evidence evaluated at an independent central reading center (*cf.* **Appendix B**, **Section 12.0**) and judged by criteria contained in ISO 11979-7:2018 Section 6.2.2.

11.1.2.2.2 Change from Baseline in UNVA

The goal of the second secondary performance evaluation is to show that uncorrected near visual acuity after cataract removal and implantation of the Test lens is superior to the near acuity achieved by the same eye in its cataractous presurgical state with its natural refractive errors. For mean change from baseline in photopic monocular logMAR UNVA in first implanted eyes in the Test lens group at Post-Operative Visit 4, the null and alternative hypotheses are as follows:

$$H_0: \mu_d \geq 0$$

$$H_1: \mu_d < 0$$

Where:

- μ_d = the mean change from baseline in photopic uncorrected near visual acuity (UNVA) for first implanted eyes in the Test lens group at 40 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye implantation)

11.1.2.2.3 Change from Baseline in UIVA

The goal of the second secondary performance evaluation is to show that uncorrected intermediate visual acuity after cataract removal and implantation of the Test lens is superior to the intermediate acuity achieved by the same eye in its cataractous presurgical state with its natural refractive errors. For mean change from baseline in photopic uncorrected intermediate visual acuity (UIVA) for first implanted eyes in the Test lens group at 66 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye implantation), the null and alternative hypotheses are as follows:

$$H_0: \mu_d \geq 0$$
$$H_1: \mu_d < 0$$

Where:
μ_d = the mean change from baseline in photopic uncorrected intermediate visual acuity (UIVA) for first implanted eyes in the Test lens group at 66 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye implantation)

11.2 Sample Size Determination

11.2.1 Primary Performance Endpoint Sample Sizes

11.2.1.1 UDVA

When the sample sizes in the Test and Control groups are 100 and 50 subjects, respectively, a two group one-sided 0.05 significance level t-test will have > 99% power to reject the null hypothesis that the test is inferior to the standard in favor of the alternative hypothesis that the treatment is non-inferior, assuming that the expected difference in means is 0, a non-inferiority margin is 0.2 and the common standard deviation is 0.15.

11.2.1.2 UNVA

A two-group t-test with a 5% two-sided significance level will have > 99% power to detect a difference in means of 0.2, assuming that the common standard deviation is 0.15, when the sample sizes in the two groups are 100 and 50, respectively (a total sample size of 150).

11.2.1.3 UIVA

A two-group t-test with a 5% two-sided significance level will have > 99% power to detect a difference in means of 0.2, assuming that the common standard deviation is 0.15, when the sample sizes in the two groups are 100 and 50, respectively (a total sample size of 150).

11.2.2 Sub-Studies

11.2.2.1 Defocus Curves

At least ten (10) Test enVista trifocal IOL subjects and ten (10) Control enVista monofocal IOL subjects will be evaluated to obtain defocus curves as described in **Appendix B, Section 9.0**, in each of the following pupil size groups: small (≤ 3.0 mm), medium (> 3.0 mm and ≤ 4.0 mm), and large (> 4.0 mm), as determined under photopic lighting conditions. The defocus curve sub-study subjects will be enrolled sequentially. If ten subjects are not available in any pupil size category for a treatment group, then the maximum number available will be used.

11.2.2.2 Contrast Sensitivity

At least approximately 50 bilaterally implanted Test trifocal IOL subjects and 25 bilaterally implanted Control monofocal IOL subjects will participate in the contrast sensitivity sub-study. Subjects who participate in the contrast sensitivity study will likely not participate in the defocus curve sub-study. Subjects who continue in the study with only one eligible eye also are likely not eligible for the contrast sensitivity sub-study. To allow for losses of up to 10%, at least approximately 56 Test trifocal IOL subjects and 28 Control monofocal IOL subjects will be enrolled in the sub-study.

11.2.3 Overall Sample Size and Adjustment for Dropouts

To allow for losses of up to 10%, approximately $\lceil 100/(1-0.1) \rceil = 112$ Test group subjects and approximately $\lceil 50/(1-0.1) \rceil = 56$ Control group subjects will be enrolled. The overall enrollment target will be approximately 168 subjects.

11.3 Analysis Populations

11.3.1 Intent-to-Treat Set

The Intent-to-Treat Set will include all subjects with at least one eye implanted with a study lens. Summaries and analyses of the ITT Set will classify subjects according to the treatment to which they were randomized.

11.3.2 Safety Set

The Safety Set will include all subjects with at least one eye implanted with a study lens. Summaries and analyses of the Safety Set will classify subjects according to the treatment received.

11.3.3 Per Protocol Set

The Per Protocol (PP) Set will include all bilaterally implanted subjects without major protocol deviations. Major protocol deviations are described in **Section 11.5.7**.

11.3.4 Patient Reported Outcome (PRO) Analytical Set

The PRO Analytical Set will include all subjects who submitted the preoperative questionnaires and at least one postoperative questionnaire.

11.4 Statistical Analysis

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Summaries for categorical variables will include the tabulation of frequencies and percentages.

Additional details will be provided in the statistical analysis plan (SAP), which will be completed and approved prior to database lock. Any changes to the plans in this clinical investigation plan will be noted in the SAP. Any changes to the analysis plans made after the SAP is approved may be documented using amendments to the SAP. Changes made after the last version of the SAP will be documented in the clinical study report.

If the Test IOL is statistically successful in all primary endpoints with success criteria, then the Test IOL will be statistically successful overall.

11.4.1 Primary Safety Analyses

11.4.1.1 All Implanted Eyes with at Least One Serious Adverse Event

The proportion of all implanted Safety Set eyes with at least one serious adverse event will be summarized using categorical summary statistics by treatment received. Each eye will be counted only once in the calculation of the rate.

11.4.1.2 Secondary Surgical Interventions Related to the Optical Properties of the IOL

Secondary surgical interventions related to the optical properties of the IOL will be defined as IOL explantation, replacement, or repositioning due to subject intolerance of visual symptoms not adequately improved by spectacle correction. The investigators will apply this definition to classify each secondary surgical intervention as either related to the optical properties of the IOL or not related to the optical properties of the IOL.

Each eye will be classified as either having undergone a secondary surgical intervention related to the optical properties of the IOL or not having undergone such an intervention. Missing data will not be imputed. Secondary surgical interventions related to the optical properties of the IOL will be summarized categorically (Yes, No) by actual treatment received for Safety Set subjects in a table. Secondary surgical interventions will be further subcategorized and summarized categorically as Exchange, Removal, Repositioning, or Other.

11.4.1.3 ISO Grid Adverse Events

Cumulative and persistent ISO grid AEs will be summarized categorically for all Test group eyes of the Safety Set by treatment. Subjects will be analyzed according to treatment received.

The numerator for each cumulative AE will be the number of all implanted Test group eyes reporting the AE at least once after surgery. The denominator for cumulative AEs will be the number of all implanted Test group eyes.

The numerator for each persistent AE will be the number of all implanted Test group eyes with the event at Visit 4 (Day 120 to Day 180 after second eye IOL implantation). The denominator for persistent AEs will be the number of all implanted Test group eyes present at Visit 4 (Day 120 to Day 180 after second eye IOL implantation).

For each ISO grid AE, a one-sided exact binomial test comparing the proportion of Test group eyes with the AE to the relevant control rate will be completed. If the resulting p-value is less than or equal to 0.05, then the null hypothesis will be rejected. If none of the null hypotheses are rejected, then the test lens will be statistically successful in these endpoints.

11.4.2 Secondary Safety Analyses

11.4.2.1 Subjects Experiencing at Least One Severe Visual Disturbance

The incidence of Safety Set subjects experiencing at least one severe visual disturbance, defined as the highest grade of severity or bothersomeness (separately) reported by subjects using the Quality of Vision (QoV) questionnaire through Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation), will be summarized using descriptive statistics by treatment.

11.4.2.2 Contrast Sensitivity

Mean photopic (with glare) and mesopic (with and without glare) contrast sensitivity at Post-Operative Visit 4 will be summarized using continuous summary statistics by lighting condition, spatial frequency, treatment group, and visit.

11.4.3 Primary Performance Analyses

11.4.3.1 Photopic Monocular UDVA

Photopic monocular uncorrected distance visual acuity (UDVA) at 4 m in first implanted eyes at Post-Operative Visit 4 will be summarized in logMAR units using continuous summary statistics by treatment group for the PP Set. Imputation of missing data is not conservative in non-inferiority testing. Therefore, missing data will not be imputed for the UDVA non-inferiority test. The treatment effect (mean Test [enVista trifocal] group IOL VA minus mean Control [enVista monofocal] group IOL VA) in logMAR units will be estimated in addition to a two-sided 90% confidence interval, using a statistical model with treatment and site as fixed factors. If the upper confidence limit (equivalent to a one-sided upper 95% confidence limit for the treatment effect) is less than 0.2 logMAR, then the Test enVista trifocal lens will be statistically non-inferior to the control enVista monofocal lens.

The previous continuous summary statistics will also be provided for the ITT Set. However, statistical success will not depend upon the results of the ITT analysis.

11.4.3.2 Photopic Monocular UNVA

Photopic monocular uncorrected near visual acuity (UNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to Day 180 after second eye IOL implantation) will be summarized using continuous summary statistics in logMAR units by treatment assignment for the first implanted eyes of ITT Set Subjects.

If there are missing ITT analysis set monocular UNVA values at Visit 4, then missing data will be imputed using the Markov chain Monte Carlo (MCMC) multiple imputation method. After imputation of missing data, the statistical hypotheses will be tested using statistical models with treatment and site as fixed factors by imputation.

An overall p-value resulting from the multiple imputation method will be estimated. The treatment effect (mean Test group IOL VA minus mean Control group IOL VA) in logMAR units will be summarized using continuous summary statistics and a two-sided 95% confidence interval. If the p-value from the multiple imputation analysis is less than or equal to 0.05 and the treatment effect is less than zero (i.e., the Test lens mean logMAR VA is superior to the mean for the control), then it will be concluded that the Test IOL is statistically successful (i.e., superior to the Control IOL) in this outcome.

The previous continuous summary statistics will also be provided for the Per Protocol Set. However, statistical success will not depend upon the results of the PP analysis.

11.4.3.3 Photopic Monocular UIVA

Photopic monocular uncorrected intermediate visual acuity (UIVA) at 66 cm in first implanted eyes will be summarized and analyzed using the methods described for UNVA.

11.4.4 Secondary Performance Analyses

11.4.4.1 IOL Rotational Stability

For the first secondary performance endpoint, success for IOL rotational stability of the enVista MX60EFH trifocal IOL will be measured using the criteria for toric IOLs as stated in ISO 11979-7:2018 Section 6.2.2. Assessment of the secondary performance standard for the MX60EFH trifocal IOL will only be evaluated if all primary performance endpoints have demonstrated statistical success. If both of the following conditions are met, then IOL rotational stability of the enVista trifocal IOL will have been confirmed:

- At least 90% of the enVista trifocal IOLs will have rotated 10° or less at Visit 4(Day 120 to Day 180 after second eye IOL implantation)
- At least 95% of the enVista trifocal IOLs will have rotated 20° or less at Visit 4(Day 120 to Day 180 after second eye IOL implantation)

11.4.4.2 Change from Baseline in Photopic Monocular UNVA

Photopic monocular uncorrected near visual acuity (UNVA) at 40 cm at Baseline, at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), and the Change from Baseline to Visit 4 will be summarized using continuous summary statistics in logMAR units

by treatment assignment for the first implanted eyes of ITT Set Subjects. A paired t-test will be used to test the statistical hypothesis for the Test lens group.

11.4.4.3 Change from Baseline in Photopic Monocular UIVA

Photopic monocular uncorrected intermediate visual acuity (UIVA) at 66 cm in first implanted eyes will be summarized and analyzed using the methods described for UNVA.

11.4.5 Subject Disposition

Enrollment status will be summarized in a table by investigator and overall. The number of randomized subjects will be summarized as well as the number and percentage of subjects that completed the entire trial, discontinued before implant, discontinued after the first implant but before the second surgery, and discontinued after the second surgery. In addition, for those subjects that did not complete the entire trial, the reason(s) for discontinuation will be summarized.

Accountability at each visit will be summarized. The accountability data will also be stratified by investigator and by treatment assignment.

Subjects and eyes in the Safety, ITT, PP, and PRO analysis sets will be summarized categorically by treatment and overall.

11.4.6 Demographics and Baseline Characteristics

Race, sex, ethnicity, and age will be presented by treatment group and overall in a Table.

11.4.7 Protocol Deviations

The number of subjects within each type of protocol deviation will be presented using discrete summary statistics.

Major protocol deviations leading to exclusion from the PP Set will include the following:

- Ineligible subjects
- Subjects who received an incorrect IOL (for example, including but not limited to incorrect treatment group or incorrect lens model)
- Subjects who have had the first implanted eye IOL explanted prior to Visit 4
- Subjects without measured values for all of the primary performance endpoints at Visit 4, assessed within the Visit 4 window
- Subjects who have received an excluded prior or concomitant treatment that is likely to interfere with visual performance at Visit 4

Prior to unmasking, other criteria for major protocol deviations may be added.

11.5 Additional Statistical Considerations

11.5.1 Handling of Missing Data

Unless otherwise specified, missing data will not be imputed.

11.5.2 Multicenter Issues

Randomization will be stratified by site.

11.5.3 Interim Analyses

No interim analyses are planned. There are no plans to stop the study early on statistical grounds.

11.5.4 Multiplicity Issues

As all primary performance endpoints with success criteria described in **Section 11.1** are required to demonstrate statistical success, adjustment for multiplicity is not necessary for these endpoints.

Statistical testing of the secondary endpoint with a success criterion (IOL rotational stability) will not be evaluated for success unless all primary endpoints with success criteria are met. Change from baseline in UNVA and UIVA are exploratory endpoints and will not be adjusted for multiplicity. Primary and secondary endpoints without success criteria will not affect the evaluation of secondary endpoints with success criteria. Therefore, adjustment for multiplicity is also not necessary for these endpoints.

Any statistical tests of endpoints that are not primary or secondary endpoints will be considered exploratory and will not be adjusted for multiplicity.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study Monitoring

The Sponsor and its representatives must be allowed to visit all study site locations to assess the data, quality, and study integrity in a manner consistent with applicable HC and local authority regulations and the procedures adopted by the Sponsor or its representative.

Prior to the start of the study, member(s) of the Sponsor (or designees) will review the protocol, CRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator/Sub-Investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur as necessary, as per the monitoring plan, during the course of the investigation to verify the following:

- The rights and well-being of subjects are protected
- The conduct of the investigation is in compliance with:
  - The content of this protocol,

- ISO 14155:2020 (E) Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice,

and in accordance with:

- ISO 11979-7:2018 Ophthalmic implants — Intraocular lenses — Part 7: Clinical investigations of intraocular lenses for the correction of aphakia,
- ISO/TR 22979 (2017) Ophthalmic implants – Intraocular lenses – Guidance on assessment of the need for clinical investigation of intraocular lens design modifications,
- ANSI Z80.12-2007 (R2017), and
- Applicable national and local medical device regulations and standards.

- The integrity of the data, including adequate study documentation
- The facilities remain acceptable
- The Investigator and site personnel remain qualified and able to conduct the study
- Test article accountability

During the study, if the Sponsor (or designee) determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor (or designee) will take remediation action to secure compliance. In addition, the Sponsor may terminate the Investigator's participation in the study, if appropriate, if the Investigator remains non-compliant despite the remediation actions.

12.2 Source Documentation

All medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real-time as it is collected. Source documentation consists of original subject documents, as well as data and records with information relevant to the subject and his/her participation in the study.

Source documentation worksheets may be provided by the Sponsor or its designee to record pertinent information. The completed worksheets can then be incorporated into the subject's medical chart. If it is preferred not to use the worksheets in the subject's permanent record, then the worksheets should be used as a reference to determine the type of study data to record in the subject's permanent record.

12.3 Case Reports Forms and Data Verification

As used in this protocol, the term Case Report Form (CRF) refers to an element of an EDC system and should be understood to refer to an electronic data record developed as part of the electronic data capture method utilized in this study.

Subject data required by this protocol are to be recorded on CRFs. The Investigator and his/her study site personnel will be responsible for completing the CRFs in a timely manner. The Investigator is required to verify that all of the requested information is accurately recorded on the CRFs. All information requested on the CRFs needs to be supplied, including subject identification and initials, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on CRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the CRFs utilizing the original and all source documentation and querying discrepant findings. The Investigator and study site personnel will be responsible for answering all queries in a timely manner.

12.4 Recording of Data and Retention of Documents

Subject data recorded on CRFs during the study will be documented in a coded fashion. The subject will only be identified by the unique subject number. Confidentiality of subject records must be maintained to ensure adherence to applicable clinical practice standards and local privacy regulations.

The Investigator must retain essential documents indefinitely after the completion of the study, unless otherwise notified by the Sponsor. The Investigator agrees to adhere to the document retention procedures when signing the protocol Investigator Statement of Approval.

Essential documents include, but are not limited to, the following:

- IRB/IEC approvals for the study protocol, all amendments, ICF(s), and advertisements
- IRB/IEC annual study review
- IRB/IEC correspondence and reports (e.g., SAE reports, protocol deviations, and safety updates)
- Regulatory documents (e.g., financial disclosure and delegation of authority forms)
- All source documents
- CRFs
- Subject's signed ICF
- Device Investigator Agreement
- Accountability records for the test article(s)
- Correspondence from and to the Sponsor and CRO
- Any other documents relevant to the conduct of the study

In the event the Investigator withdraws from the study (e.g., retirement or relocation), study records will be transferred to a mutually agreed upon designee (e.g., another Investigator or the site IRB/IEC). The Investigator will provide notice of such transfer in writing to the Sponsor and/or its representative.

12.5 Audits and Inspections

Audits of clinical research activities in accordance with the Sponsor's internal Standard Operating Procedures (SOPs) to evaluate compliance with ISO 14155:2020 and the principles of GCP may take place. A regulatory authority also may wish to conduct an inspection during the study or after its completion. If an inspection is requested by a regulatory authority and/or IRB/IEC, the Investigator must inform the Sponsor and its representative immediately that this request has been made.

13 ETHICS AND ADMINISTRATIVE ISSUES

It is the responsibility of the site's principal investigator to assure that all aspects of the ethics review are conducted in accordance with ISO 14155: 2011. The protocol and any information supplied to the subject to obtain informed consent, including written informed consent form(s), subject recruitment procedures (e.g., advertisements), and written information to be provided to subjects (information leaflets), will be reviewed and approved by a qualified IRB/IEC prior to enrollment of participants in the study. Prior to initiation of the study and release of test articles to a clinical site, the Sponsor or its designee will receive documentation of the IRB/IEC approval, which specifically identifies the approved study/protocol and a list of the IRB/IEC committee members. Protocol amendments will be reviewed and approved by the IRB/IEC prior to implementation of any changes made to the study design in the amendment. Investigators will submit progress reports to the IRB/IEC in accordance with the IRB/IEC requirements.

13.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and ISO 14155, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki.

13.2 Ethics Review

The Investigator should ensure his/her participation in the study, the protocol, subject recruitment materials (e.g., written information or materials including web pages, radio advertisements, television spots or written text developed to encourage subject enrollment) and the ICF to be used in this study are approved by his/her institution IRB/IEC, or, if not using his/her institution's IRB/IEC, by the reviewing central IRB/IEC prior to entering any subjects in the study. Documentation of IRB/IEC approval of the study protocol and informed consent must be provided to the Sponsor and any designee prior to initiation of the study. In addition, the Investigator must ensure that the reviewing IRB/IEC has provided approval for any protocol amendments prior to their implementation. If the amendment necessitates a revision to the ICF, the Investigator should ensure the revised form is also submitted to and approved by the Sponsor or its designee and the IRB/IEC prior to its implementation.

13.3 Written Informed Consent

Before entry into the study, the Investigator or an authorized member of the investigational staff will explain to potential subjects (or their legally acceptable representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. The subject (or legally acceptable representative) will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent will be appropriately recorded by means of either the subject's or his/her legally acceptable representative's dated signature. After having obtained the consent, a copy of the signed and dated ICF will be given to the subject.

If the subject (or legally acceptable representative) is unable to read or write, an impartial witness will be present for the entire informed consent process (which includes reading and

explaining all written information) and will personally date and sign the ICF after the oral consent of the subject (or legally acceptable representative) is obtained.

The informed consent form will be signed before the performance of any study-related activity.

During the study, if any new information becomes available that may affect the participation of the subject in the study, the subject will be contacted and informed. A revised consent form may be required to be signed by the subject to continue participation in the study.

13.4 Financial Disclosure

An original financial disclosure Form (FDF) must be completed, signed and dated by the PI and any sub-investigators and study personnel listed on the Delegation of Authority Log. A copy of all FDFs will be collected by the Sponsor or its designee and filed in the study Trial Master File. All original FDFs will be retained in the Investigator Site Binder.

13.5 Confidentiality/Publication of the Study

All study data generated as a result of this study will be regarded as confidential until appropriate analysis and review by the Sponsor or its designee and the Investigator(s) are completed. The clinical investigation will be registered in a publicly available database. The results of the study may be published or presented by the Investigator(s) after the review by, and in consultation and agreement with, the Sponsor, and such that confidential or proprietary information is not disclosed. Authorship will be determined based on the recommendations set forth by the International Committee of Medical Journal Editors (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). In addition, the results of the study will be published in a publicly available database.

Prior to any publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee, for comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to Bausch & Lomb Incorporated products and activities receive fair, accurate, and reasonable presentation.

13.6 Retention of Records

Study Site and Principal Investigator shall comply with all recordkeeping Health Canada's requirements and shall retain each Subject's Study records, which include the Study Site's copies of all Study data as well as relevant source documents, under storage conditions conducive to their stability and protection, for a period of 25 years after termination of the study, and to allow for inspection of all such records including the Subjects' medical records by Regulatory Authorities, or Sponsor or their designees.

14 REFERENCES

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15 APPENDICES

Appendix A STUDY FLOW CHART

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to Day 180 Post Visit 00B
Informed Consent	X									
Demographics	X									
Ocular and Non-Ocular Medical History	X									
Inclusion/Exclusion	X	X[b]				X[b]				
Patient Reported Outcome Questionnaires [c]	X									X
Potential Visual Acuity	X									
Corneal Topography	X									
Targeted Refraction / IOL Power Calculation / Axial Length Determination/Anterior Chamber Depth	X									
Chord length µ	X									X
Keratometry	X				X				X	X

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to Day 180 Post Visit 00B
Manifest Refraction (ETDRS)	X			X	X			X	X	X
Randomization	X[e]									
Operative Procedures		X				X				
Photopic Pupil Size	X								X[d]	X
Mesopic Pupil Size	X									X
UDVA – photopic, monocular	X				X				X	X
CDVA – photopic, monocular	X			X	X			X	X	X
UNVA[f] – photopic, monocular	X				X				X	X
DCNVA[f] – photopic, monocular	X				X				X	X
UIVA[g] – photopic, monocular	X				X				X	X
DCIVA[g] – photopic, monocular	X				X				X	X
UNVA[f] – photopic, binocular									X	X
UIVA[g] – photopic, binocular									X	X
UNVA[f] – mesopic, binocular	X				X				X	X
UIVA[g] – mesopic, binocular	X				X				X	X

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to Day 180 Post Visit 00B
Binocular corrected distance contrast sensitivity testing (photopic with glare at 3, 6, 12 and 18 cpd)[h]										X
Binocular corrected distance contrast sensitivity (mesopic with and without glare at 1.5, 3, 6, and 12 cpd)[h]										X
Binocular CDVA Defocus Curves[h]										X
Intraocular Pressure	X		X	X	X		X	X	X	X
Slit-Lamp Exam[i]	X		X	X	X		X	X	X	X
Pharmacologic Pupil Dilation[j]	X				X				X	X[k]
Dilated Fundus Exam	X				X				X	X[k]
Photography for rotational stability assessment[l]		X	X		X	X	X		X	X
Posterior capsulotomy assessment			X	X	X		X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X

[a] Must occur before Operative Visit 00B

[b] Review of inclusion/exclusion criteria prior to surgery

[c] To additionally be completed at any post-operative Unscheduled Visit and prior to unscheduled study exit (e.g., IOL explanation).

[d] Completed for both eyes. Also see footnote j.

[e] Subjects will be randomized following determination of eligibility based on meeting all inclusion criteria and none of the exclusion criteria.

[f] Distance to be 40 cm

[g] Distance to be 66 cm

[h] Conducted on a subset of subjects

[i] Includes determination of medical and lens findings/complications, including decentration, tilt and PCO (note: lens findings/complications, including decentration, tilt and PCO evaluated post-operatively only).

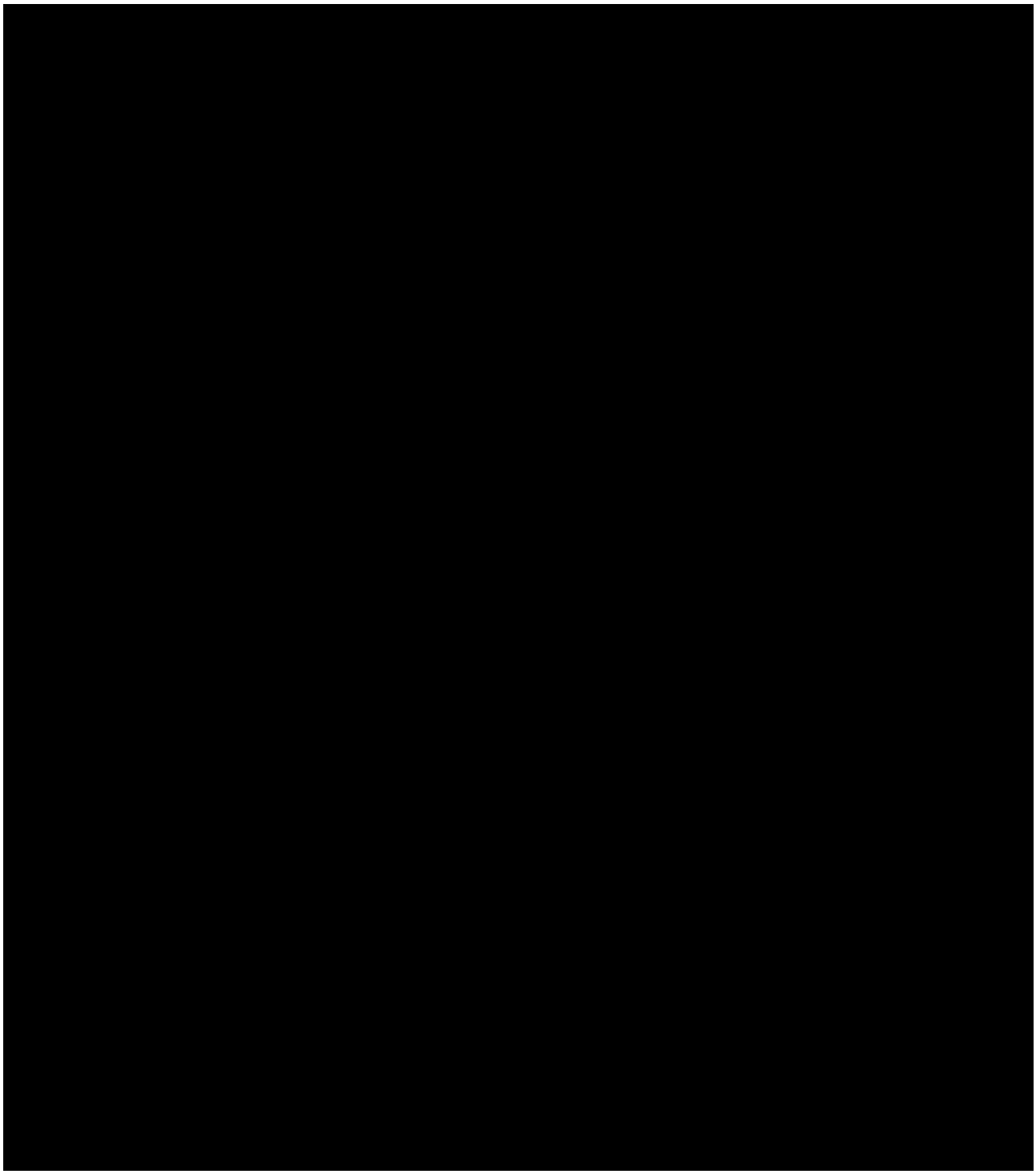
[j] Assessment for minimum pupil size of 5.0 mm in both eyes following pharmacologic pupil dilation with mydriatic agents is only performed at the pre-operative visit after all procedures listed in Appendix A prior to pharmacologic pupil dilation are completed.

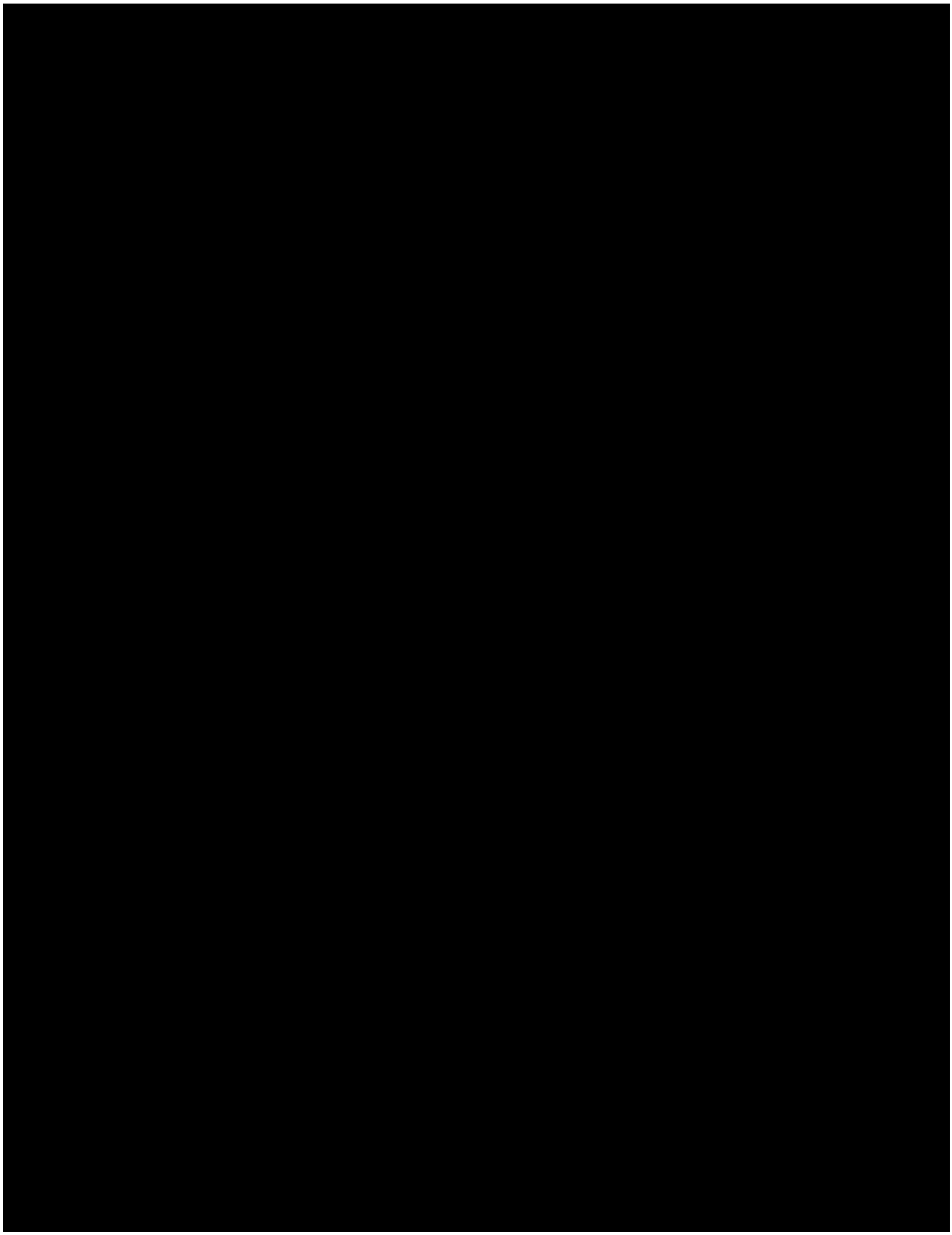
[k] If clinically indicated

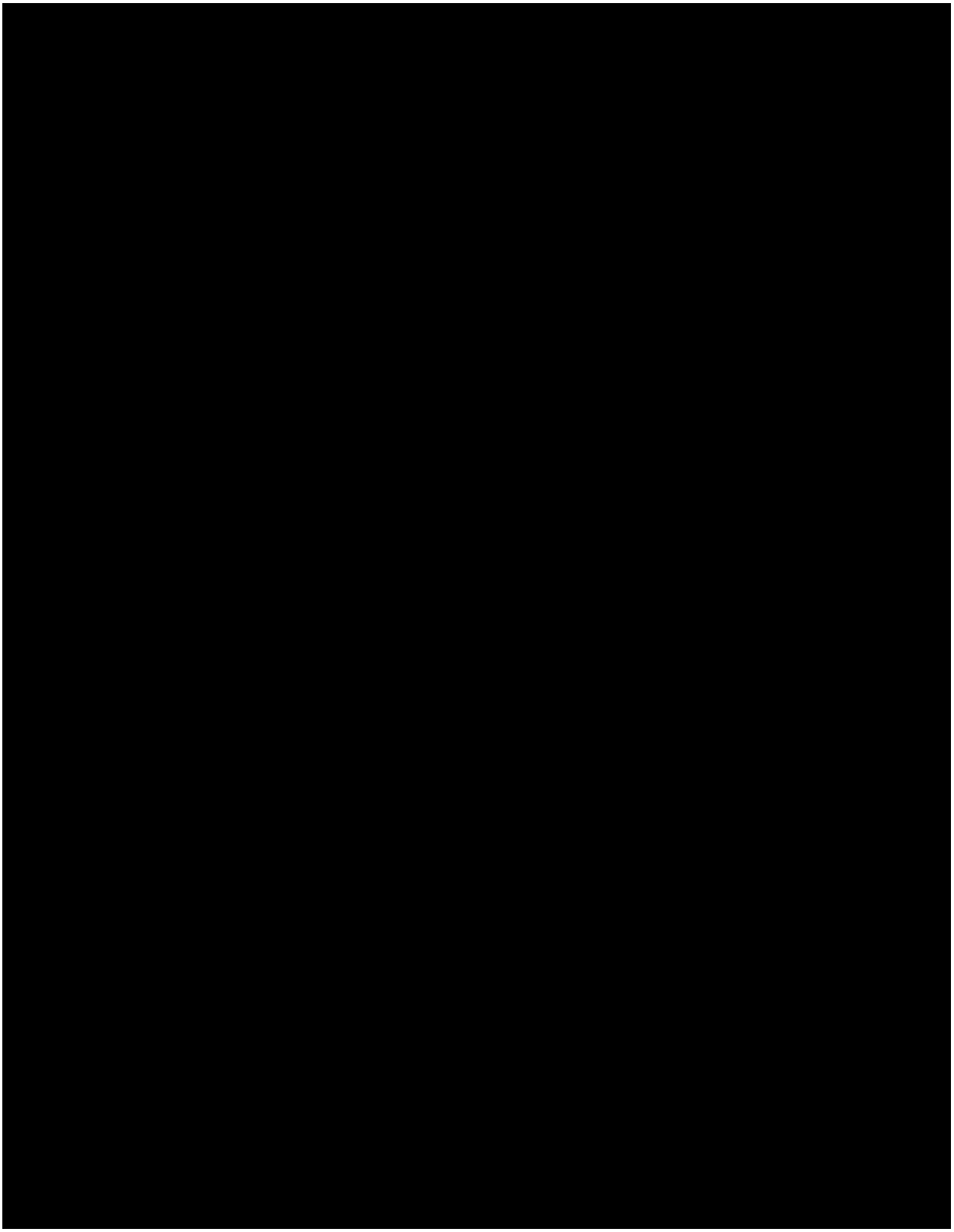
[l] Photograph are to be taken for all subjects to maintain masking of the assigned IOLs for subjects. Photographs will be sent to a central reading center for assessment of rotational stability for eyes implanted with trifocal IOLs. In addition, Investigators may elect to also take intraoperative photographs for placement of IOLs.

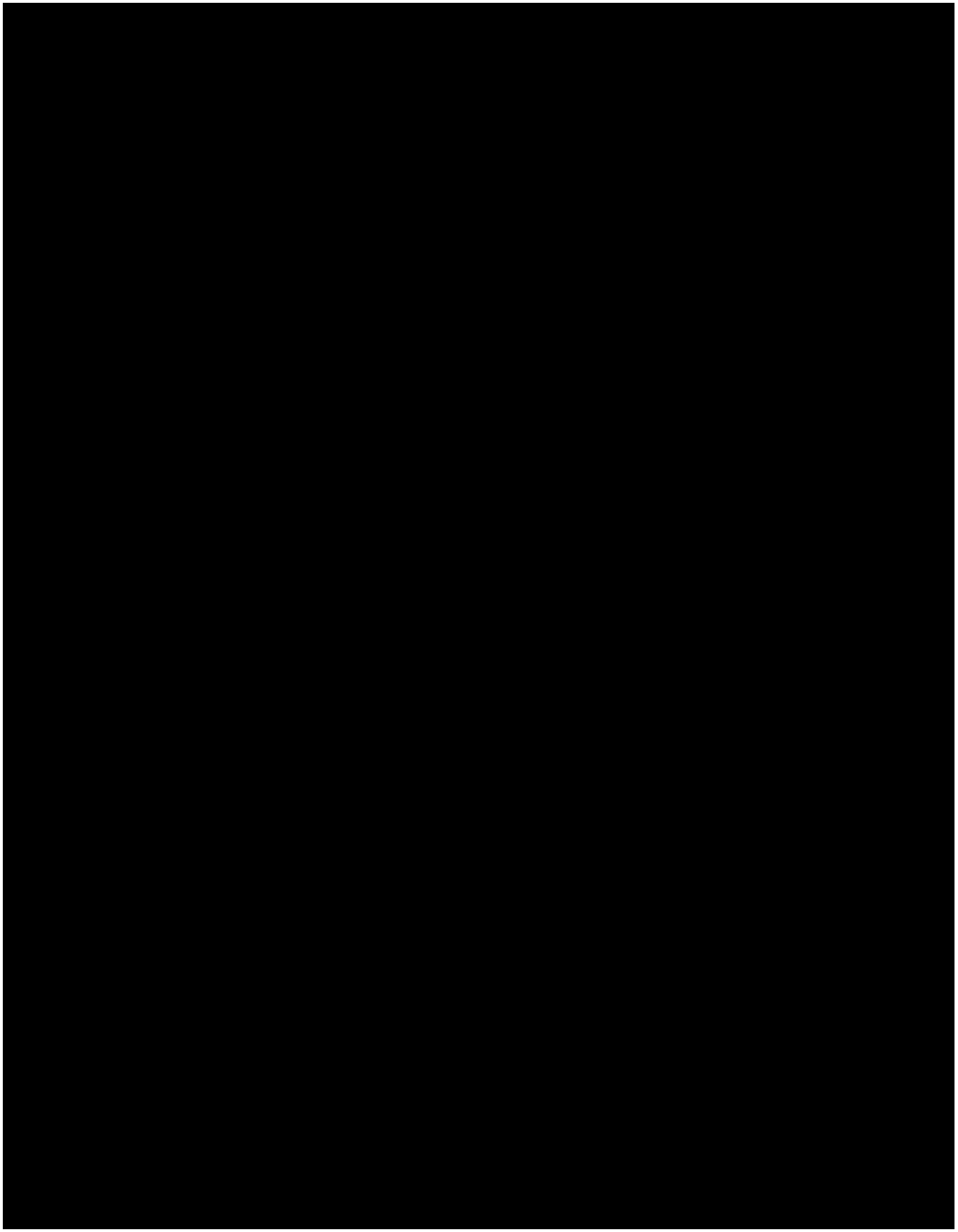
Appendix B METHODS OF CLINICAL EVALUATIONS

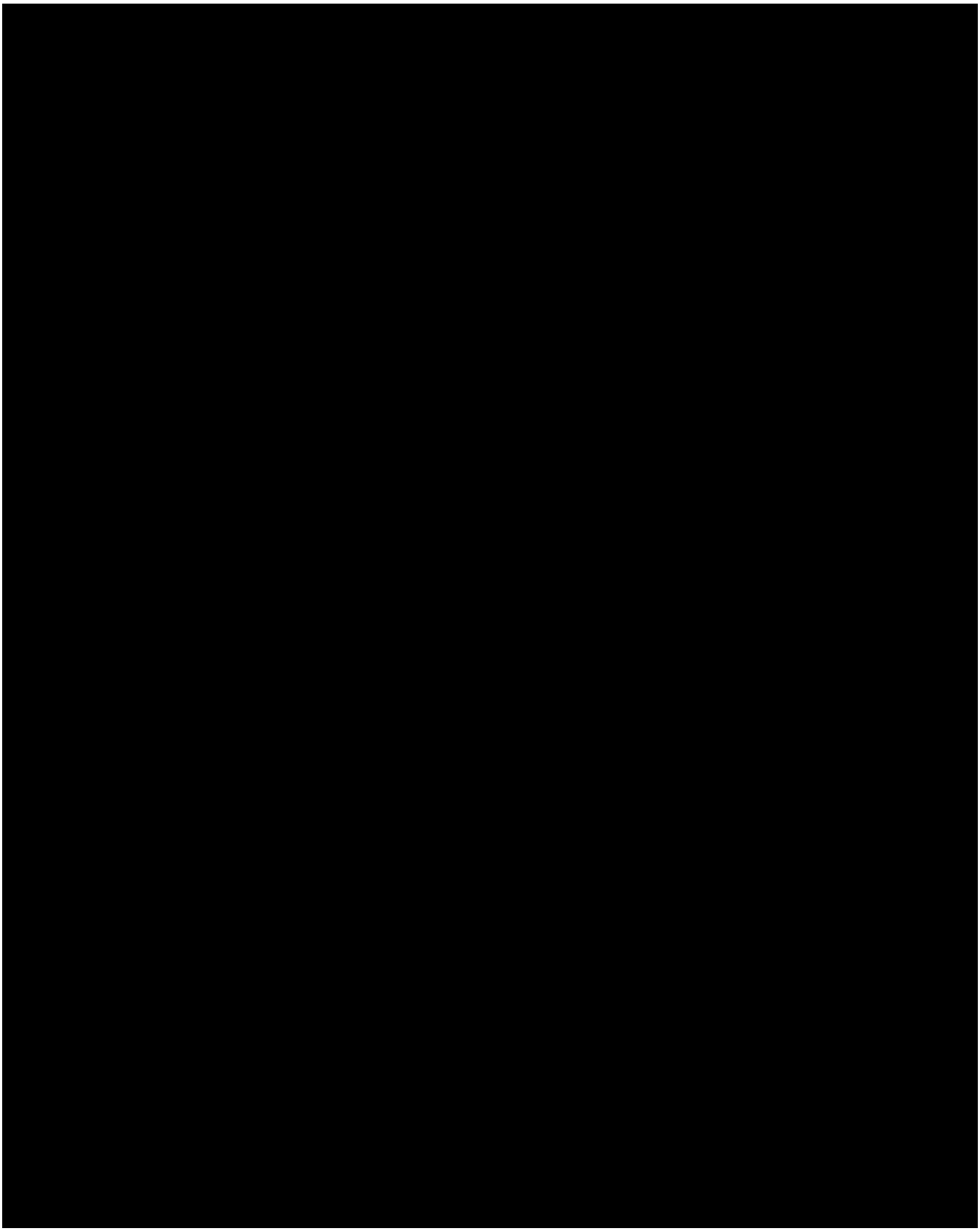
Any changes to the procedures described in this appendix will be provided under separate cover. Such changes will be documented in a CIP amendment and approved by the relevant IRB/IEC if deemed a substantial procedure modification prior to their implementation.

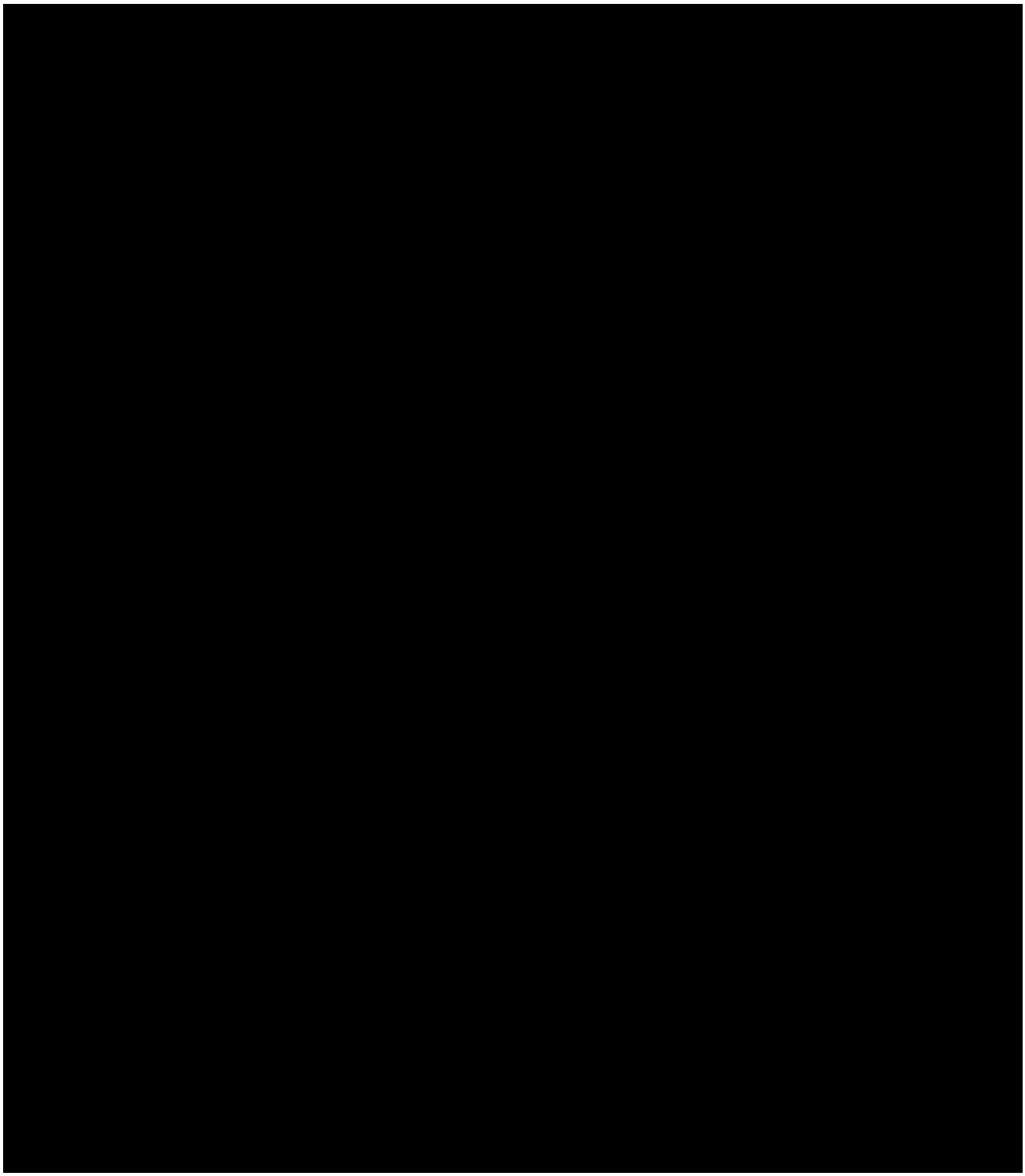


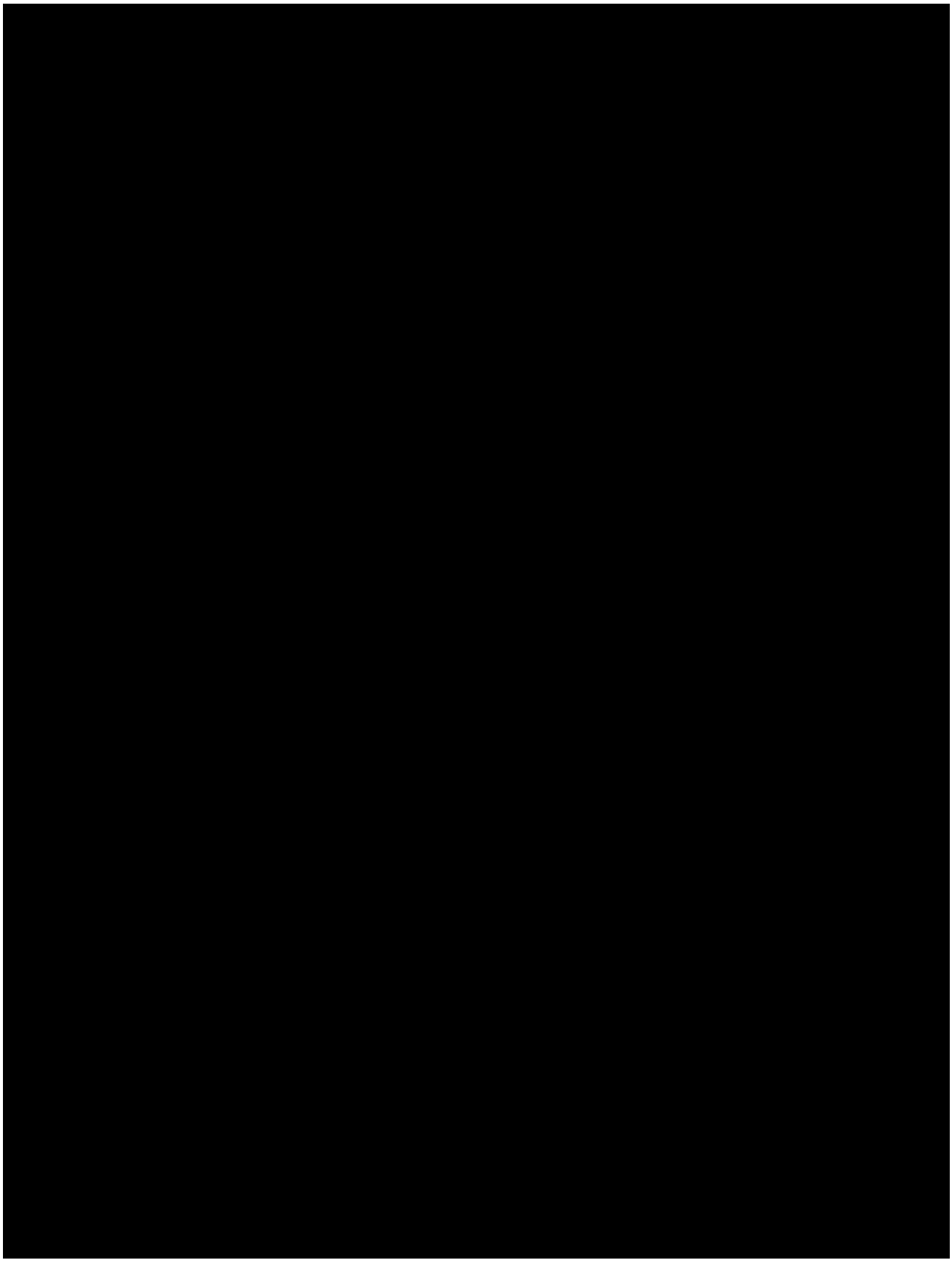


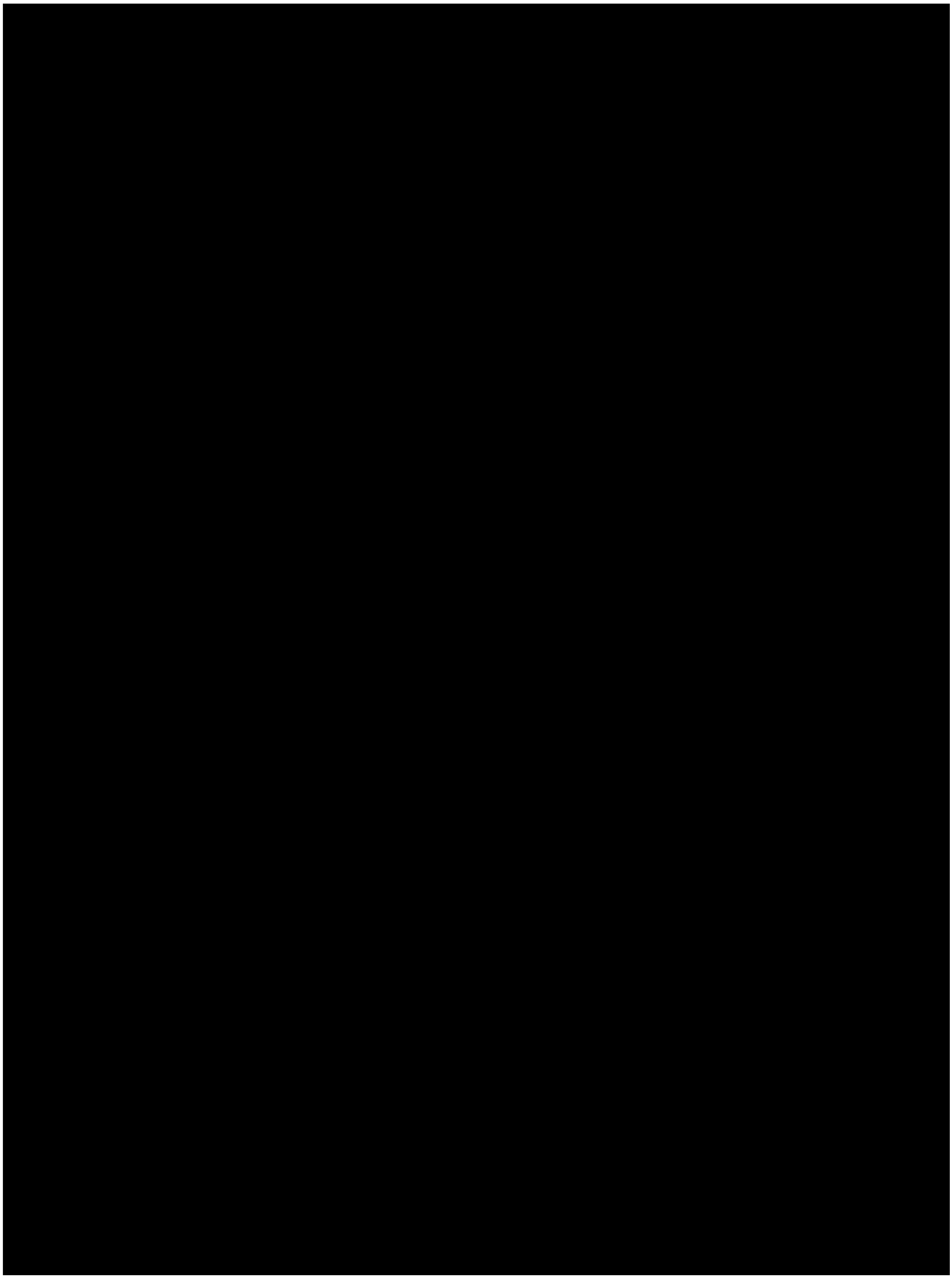


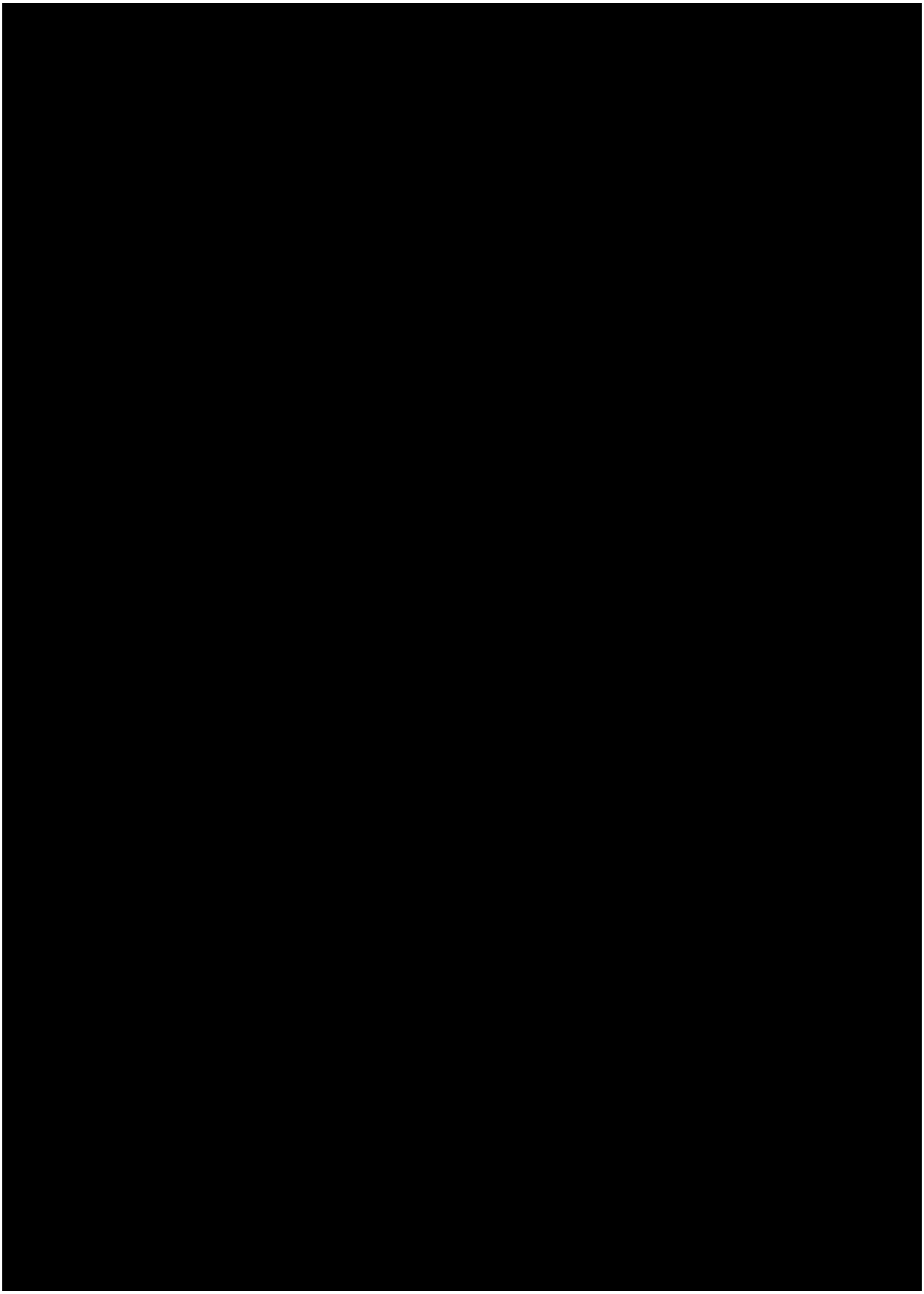


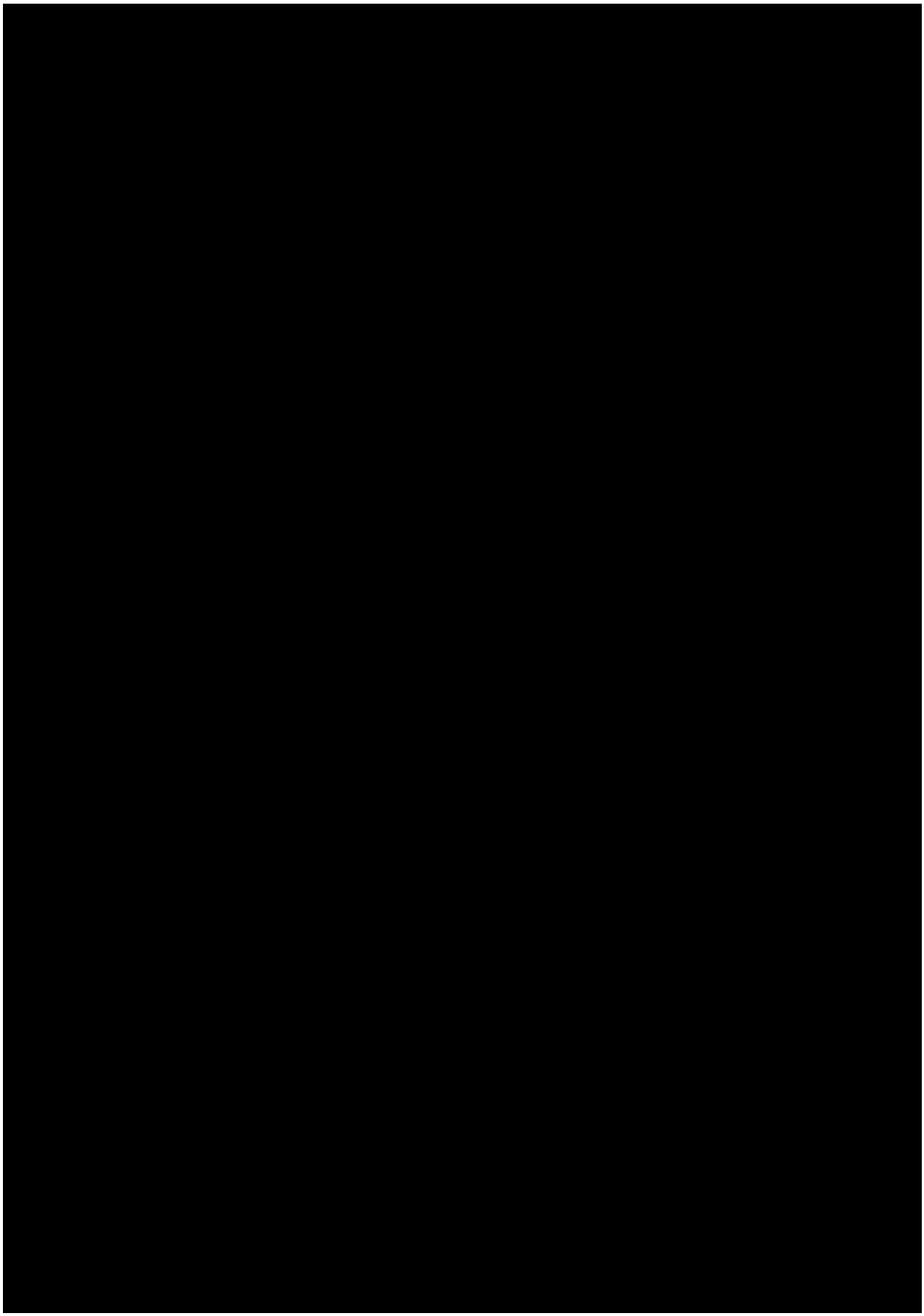


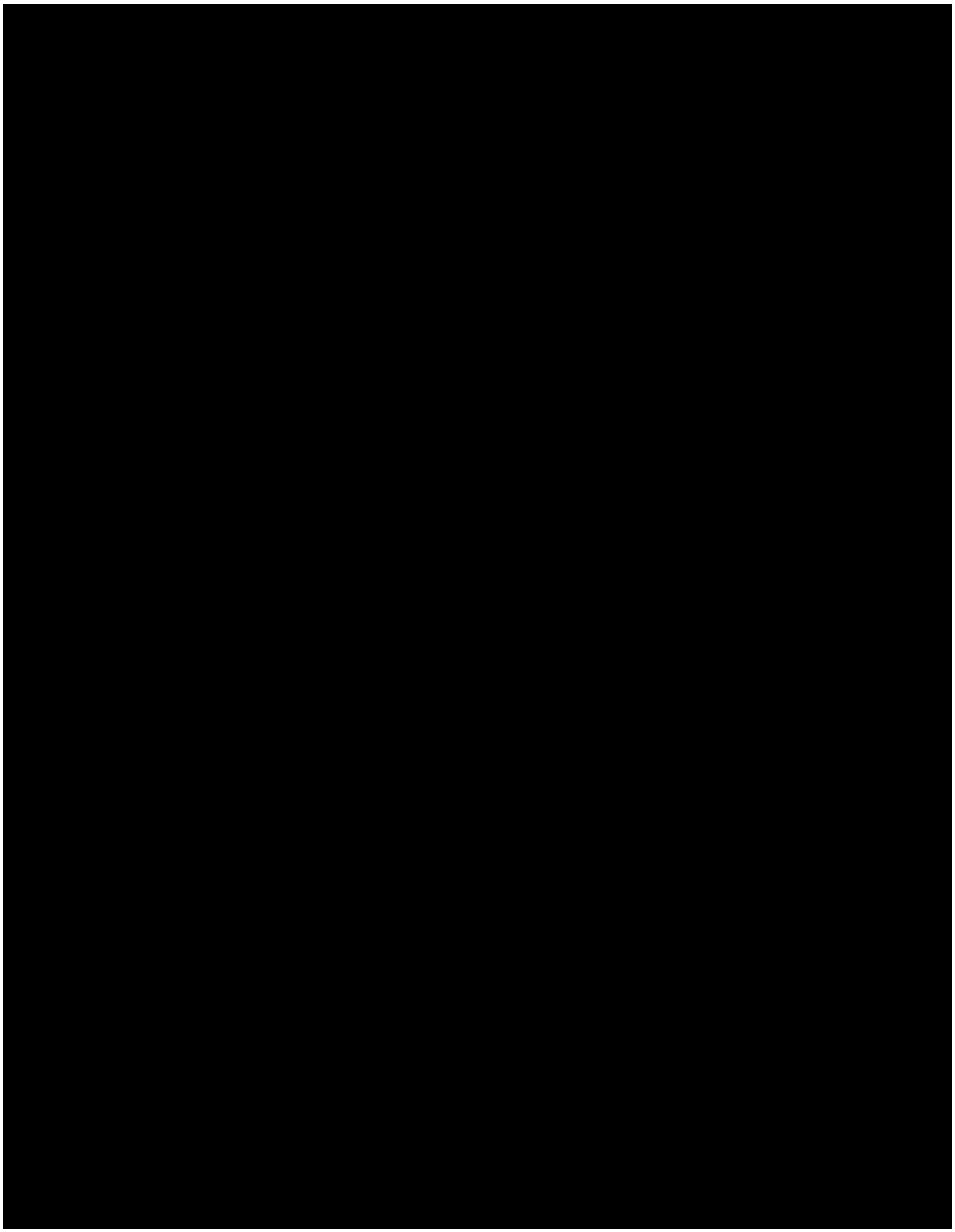










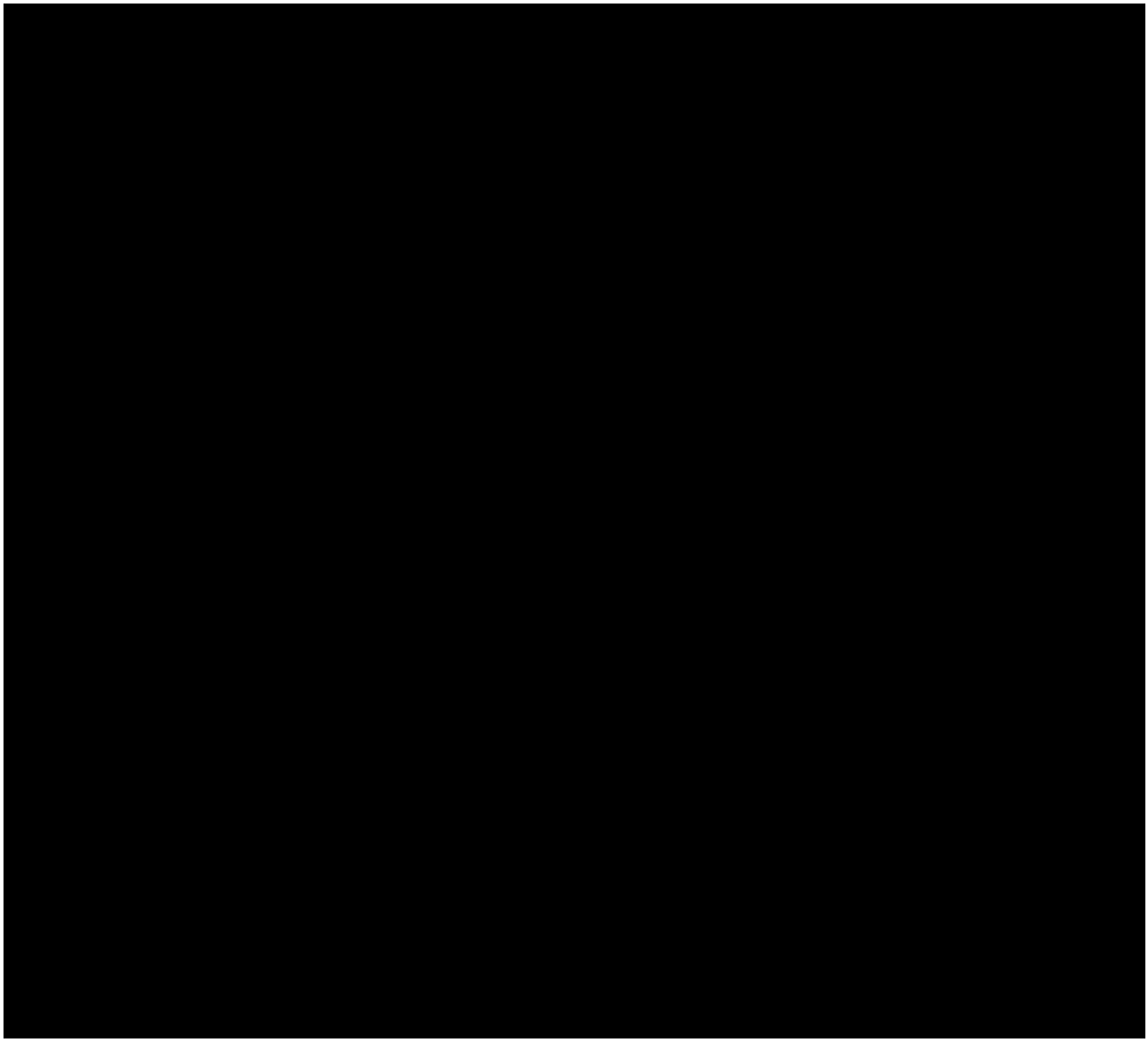


Appendix C: SURGICAL PROCEDURE

All cataract surgical procedures will be performed by a qualified Investigator, using a phacoemulsification system adjusted according to the surgeon's usual settings (power modulation should be used).

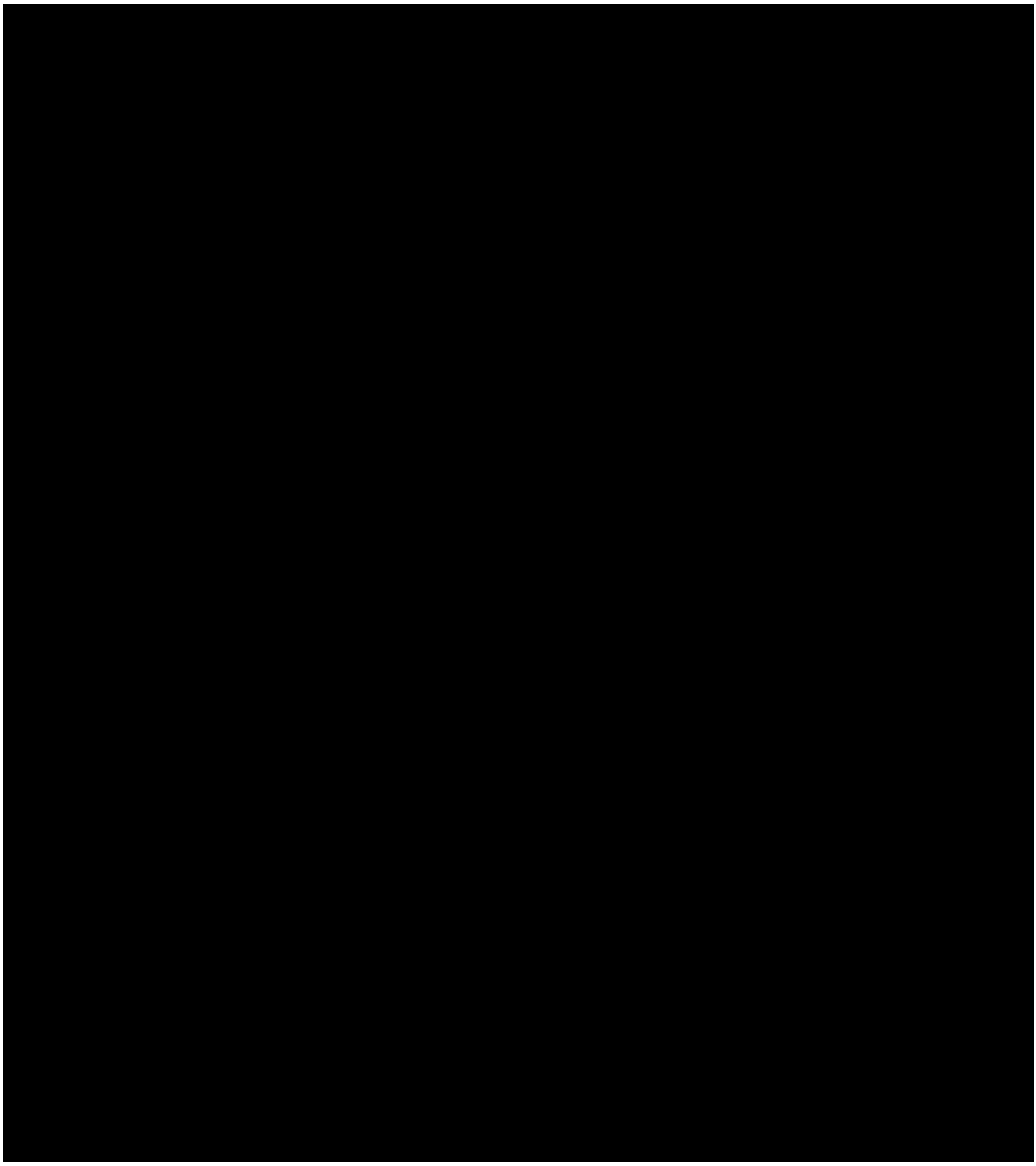
Surgery to implant the study IOLs will be performed on Day 0 of the study for the first eye and Day 7 to Day 30 for the second eye, using standard microsurgical techniques. Surgery will be performed under either local or topical with or without intracameral ophthalmic anesthesia.

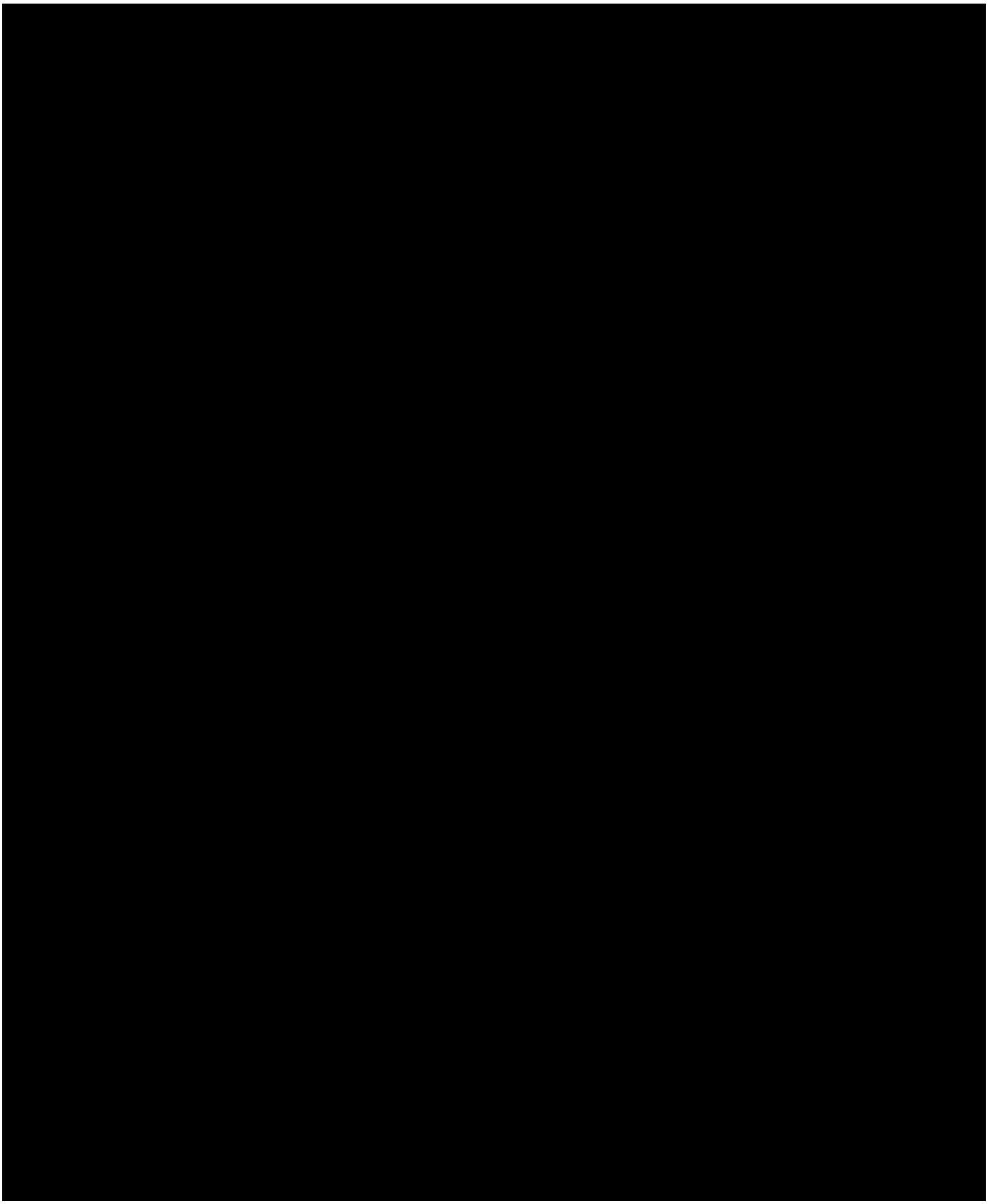
A viscoelastic (Amvisc® Plus) should be used for the procedure. If the investigator determines that a supplemental ophthalmic viscoelastic device (OVD) is necessary, based on individual subject conditions or surgical circumstances, the use of a commercially available dispersive OVD will be permitted. In such cases, the investigator should document the reason for use of a supplemental OVD in the source document along with Amvisc Plus.

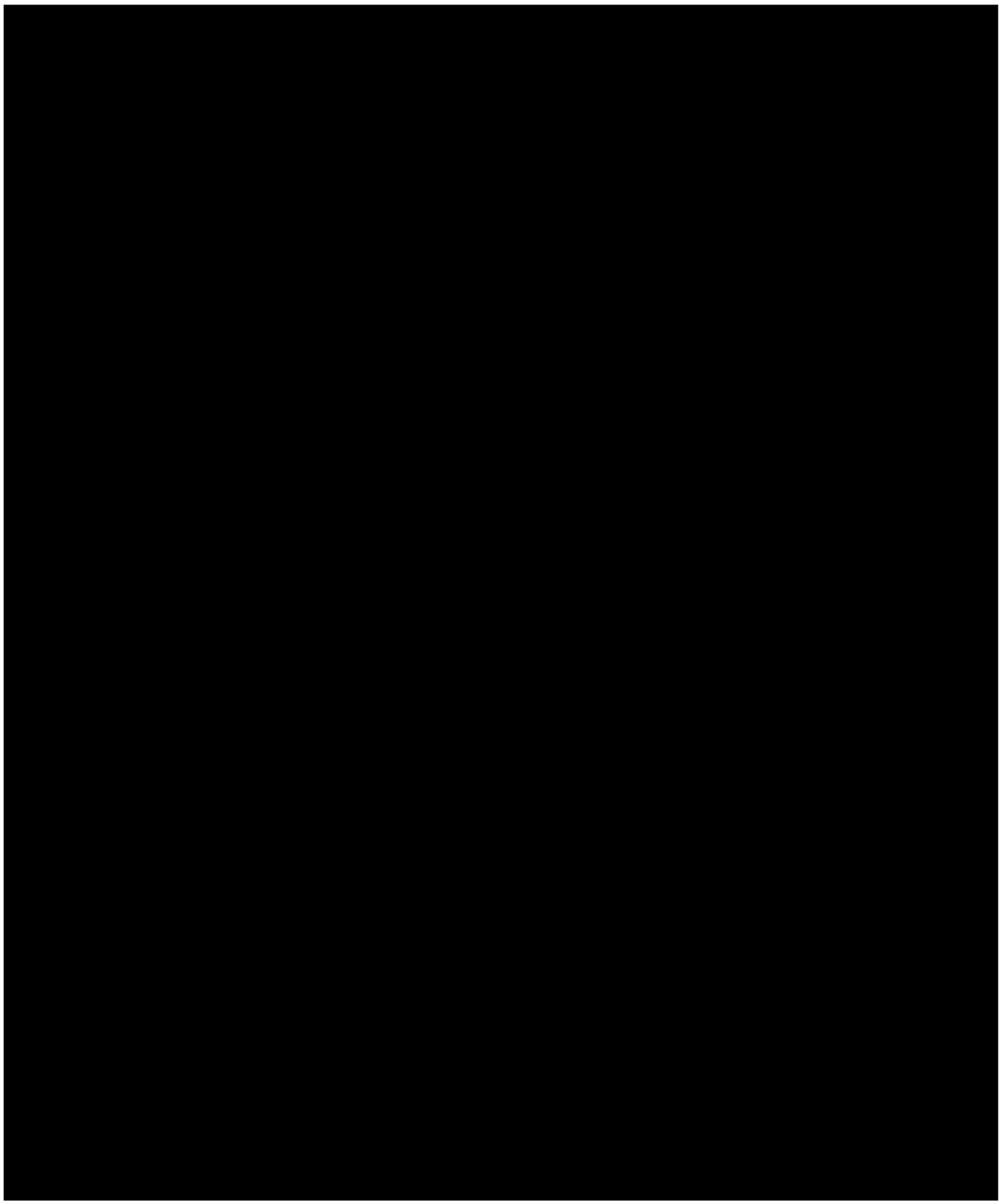


Appendix D: PATIENT REPORTED OUTCOME QUESTIONNAIRES

1. Quality of Vision (QoV) Questionnaire







2. THE NEAR ACTIVITY VISUAL QUESTIONNAIRE (NAVQ)