Short Title:

**Statistical Analysis Plan
ILX140-P001 / NCT04528069**

Full Title:

**Statistical Analysis Plan
ILX140-P001**

Protocol Title:	Clinical Investigation of the Visual Outcomes and Safety of AcrySof® IQ PanOptix® Toric Trifocal IOLs in Asian Population
██████████████	██████
Protocol TDOC Number:	TDOC-0057199
█████	██████
	████████
Approvals:	See last page for electronic approvals.
Job Notes:	

This is the first revision (Version 2.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 1.0 of the study protocol.

Executive Summary:

Key Objectives:

To evaluate the clinical performance of the ACRYSOF® IQ PanOptix® Toric Trifocal intraocular lenses (Model TFNT30, TFNT40, TFNT50, TFNT60) when implanted to replace the natural lens following cataract removal in Asian Population.

Decision Criteria for Study Success:

Not Applicable.

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List of Tables

1   Study Objectives and Design

1.1   Study Objectives

Primary Effectiveness objectives

Primary Effectiveness objectives are to describe the following at Month 3 and Month 6 for all operative eyes:

- Residual manifest cylinder
- IOL rotational stability
- Binocular Best Corrected Distance Visual Acuity (BCDVA) (4 m from spectacle plane) in photopic lighting
- Binocular Distance Corrected Intermediate Visual Acuity (DCIVA) (60 cm from spectacle plane) in photopic lighting
- Binocular Distance Corrected Near Visual Acuity (DCNVA) (40 cm from spectacle plane) in photopic lighting

Safety objectives

Safety objectives are to describe the following at Month 3 and Month 6 for all operative eyes:

- Estimate the cumulative rate of secondary surgical interventions (SSIs)
- Evaluate the rates of severe and most bothersome visual disturbances using the QUVID questionnaire
- Evaluate the rates of adverse events

1.2   Study Description

Key components of the study are summarized in Table 1-1.

Table 1-1   Study Description Summary

Investigational products	ACRYSOF® IQ PanOptix® Toric Trifocal Intraocular Lenses (IOLs) (Models: TFNT30, TFNT40, TFNT50, TFNT60)
Study Design	Prospective, unmasked, single arm, multi-center, postmarket study; total duration of a subject's participation is approximately 8 months.
Subject population	Adult Asian subjects, 20 years of age or older, who self-identify as being of Chinese, Japanese, Korean, or Mongolian descent, who require bilateral cataract extraction by phacoemulsification and have pre-existing

	corneal astigmatism, desire an IOL that provides the potential correction for near, intermediate and distance vision, as well as, pre-existing corneal astigmatism. Planned number of subjects enrolled/consented: 63 subjects Planned number of implanted subjects: 56 subjects Planned number of completed subjects: 50 subjects
Number of Sites	Approximately 4-5 sites in Australia
Visits	Visit 0: Pre-operation Visit 00/00A: Operation Visit 1/1A: Day 1-2 Visit 2/2A: Day 7-14 Visit 3A: Day 30-60 Visit 4A: Day 90-120 Visit 5A: Day 180-210

1.3   Randomization

Not applicable. This is a single arm, unmasked study.

1.4   Masking

This is an open-label study. Treatment assignment may be known to the investigators, subjects or Alcon personnel involved with the planning and execution of the study.

2   Analysis Sets

All subjects will be considered enrolled once they have signed the informed consent form. Subject evaluability will be determined prior to the ███████████████████████ final database lock, based upon the Deviations and Evaluability Plan (DEP).

2.1 Efficacy Analysis Sets

All-Implanted Analysis Set (AAS) includes all eyes with successful IOL implantation with at least one post-operative visit. The AAS will be the primary analysis set for all effectiveness analyses ███████████

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2.2 Safety Analysis Set

The Safety Analysis Set (SS) will include all eyes with attempted IOL implantation (successful or aborted after contact with the eye). The SS will be the primary set for all safety analyses.

3 Subject Characteristics and Study Conduct Summaries

Subject characteristics and study conduct summaries will include tables and listings such as a subject disposition table, demographics (age, sex, race, specific Asian nationality) and baseline characteristics tables (BCDVA, axial length, anterior chamber depth, corneal astigmatism, etc.). Listing of discontinuation, and listing of evaluability and protocol deviations will be provided.

All summary statistics will be based on the type of variable. For categorical variables, such as sex, age group (< 65 years; ≥ 65 years), race and specific Asian nationality, the number and percentage of eyes/subjects in each category for non-missing data will be presented. For continuous variables, the number of non-missing eyes/subjects, mean, standard deviation, median, minimum, and maximum values will be presented.

4 Efficacy Analysis Strategy

4.1 Efficacy Endpoints

All effectiveness endpoints will be summarized as follows for each visit, with Month 3 and 6 visit results being the key endpoint.

Key Endpoints

- Mean monocular residual manifest cylinder for all operative eyes

- Percent of IOLs with < 10 degree rotation for all operative eyes (rotation defined as the difference in IOL axis of orientation from postoperative day 1)

- Mean binocular BCDVA at 4m in photopic lighting condition

- Mean binocular DCIVA at 60cm in photopic lighting condition

- Mean binocular DCNVA at 40 cm in photopic lighting condition

4.2   Efficacy Hypotheses

No formal statistical hypothesis testing is planned for any endpoints. Rather, the data will be summarized using descriptive statistics.

4.3   Statistical Methods for Efficacy Analyses

4.3.1   Analysis of Key Effectiveness Endpoints

4.3.1.1   Residual Manifest Cylinder

Monocular residual manifest cylinder will be summarized by visit for first operative eye, second operative eye and all eyes. The descriptive statistics including the number of eyes, mean, median, standard deviation, minimum, maximum, and two-sided 95% CI of the mean will be presented. Additionally, the number and percent of eyes will be presented for residual manifest cylinder in the following categories: within 0.25 D, within 0.50 D, within 1.00 D and more than 1.00 D.

4.3.1.2   IOL Rotation

IOL rotation is defined as the difference in IOL axis of orientation from postoperative day 1. IOL rotation will be summarized by sample size, number, percent, and cumulative percent for the following categories of absolute rotation: <5, < 10, < 20 and ≥ 20 degrees. Additionally, descriptive statistics including the number of eyes, mean, median, standard deviation, minimum, maximum, and two-sided 95% CI of the mean will be reported for absolute value of IOL rotation. A listing of eyes with absolute IOL rotation of 10 degrees or more will also be presented.

4.3.1.3   Binocular Photopic BCDVA, DCIVA and DCNVA

Binocular photopic BCDVA, DCIVA and DCNVA will be summarized as continuous variables with number of subjects, mean, median, standard deviation, minimum, maximum, and two-sided 95% confidence interval for the mean based on Student's t statistics, and will be presented at each visit the endpoints are collected. SAS PROC MEANS will be used to generate the confidence interval with option ALPHA=0.05.

For all visual acuity endpoints, the number and percentage of subjects in each of the following visual acuity categories will be presented:

The number and percentage of eyes with visual acuity of

- 0.00 logMAR or better: ≤0.00 logMAR

- 0.10 logMAR or better: ≤0.10 logMAR

- 0.20 logMAR or better: ≤0.20 logMAR

- 0.30 logMAR or better: ≤0.30 logMAR

- Worse than 0.30 logMAR: > 0.30 logMAR

[REDACTED]

[REDACTED]

5 Safety Analysis Strategy

5.1 Safety Endpoints

Key Endpoints:

- Rate of SSIs (including rate of SSIs related to optical properties of the IOL and rate of all SSIs)

- Rates of severe and most bothersome (separately) visual disturbances reported by QUVID questionnaire for subjects with binocular implantation by visit

- Rates of adverse events

[REDACTED]

[REDACTED]

5.2 Safety Hypotheses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of the safety endpoints listed in Section 5.1.

5.3 Statistical Methods for Safety Analyses

5.3.1 Secondary Surgical Interventions

The number and percentage of secondary surgical interventions (SSIs) will be presented for first implanted eyes, second implanted eyes and for all eyes combined in each of the following categories relative to the relationship to IOL:

1) Overall
2) Related to IOL - due to optical properties
3) Related to IOL - not due to optical properties
4) Unrelated to IOL

A listing of SSIs will be presented. The listing will include all SSI data with the following variables: Lens model, subject, age, sex, race, specific Asian race, surgery eye, eye, days from surgery, relationship, and description.

5.3.2 Questionnaire for Visual Disturbances (QUVID)

Descriptive summaries (counts and percentages) for rates of severe and most bothersome (separately) visual disturbances as reported by the subjects using the QUVID questionnaire will be presented per user manual. These rates will be accompanied by two-sided 95% CIs.

The number and percentages of subjects in each category of responses to each question on the QUVID questionnaire will be reported at each visit this questionnaire is administered per user manual.

A listing of subjects with severe or most bothersome visual disturbance at any postoperative visit will be presented. A listing of subjects with other visual symptom not mentioned in the QUVID will also be presented.

5.3.3   Adverse Events

All adverse events (AEs) occurring from when a subject signs informed consent to when a subject exits the study will be accounted for in the reporting. Summary tables for AEs will include the number of affected eyes/subjects, percentage of affected eyes/subjects, 95% two sided confidence intervals, and the number of events. The number and percentage of ocular AEs will be provided for first and second operative eyes and for all eyes. An eye/subject with multiple AEs of the same preferred term will be counted only once toward the total of this preferred term. Listings of AEs will include the lens model, subject ID, Age/Sex, days from surgery, adverse event description, the MedDRA preferred term of the adverse event, and the causality assessment, severity, duration and outcome, when available. Surgery eye and the eye with AE will be provided in the listing of ocular AEs. Adverse events related to the IOL are referred to as adverse device effects (ADE). Listing of pre-treatment AEs, or AEs for non-study eyes will be provided if such cases exist.

Treatment emergent adverse events will be summarized in the following tables and listings:

- Table of All Adverse Events (Serious and Non-Serious Combined)

  o Ocular
  o Non-ocular

- Table of All Adverse Device Effects

  o Ocular
  o Non-ocular

- Table of All Serious Adverse Events (including Serious Adverse Device Effects)

  o Ocular
  o Non-ocular

- Listing of Adverse Event

  o Serious Ocular
  o Serious Non-ocular
  o Non-Serious Ocular
  o Non-Serious Non-ocular
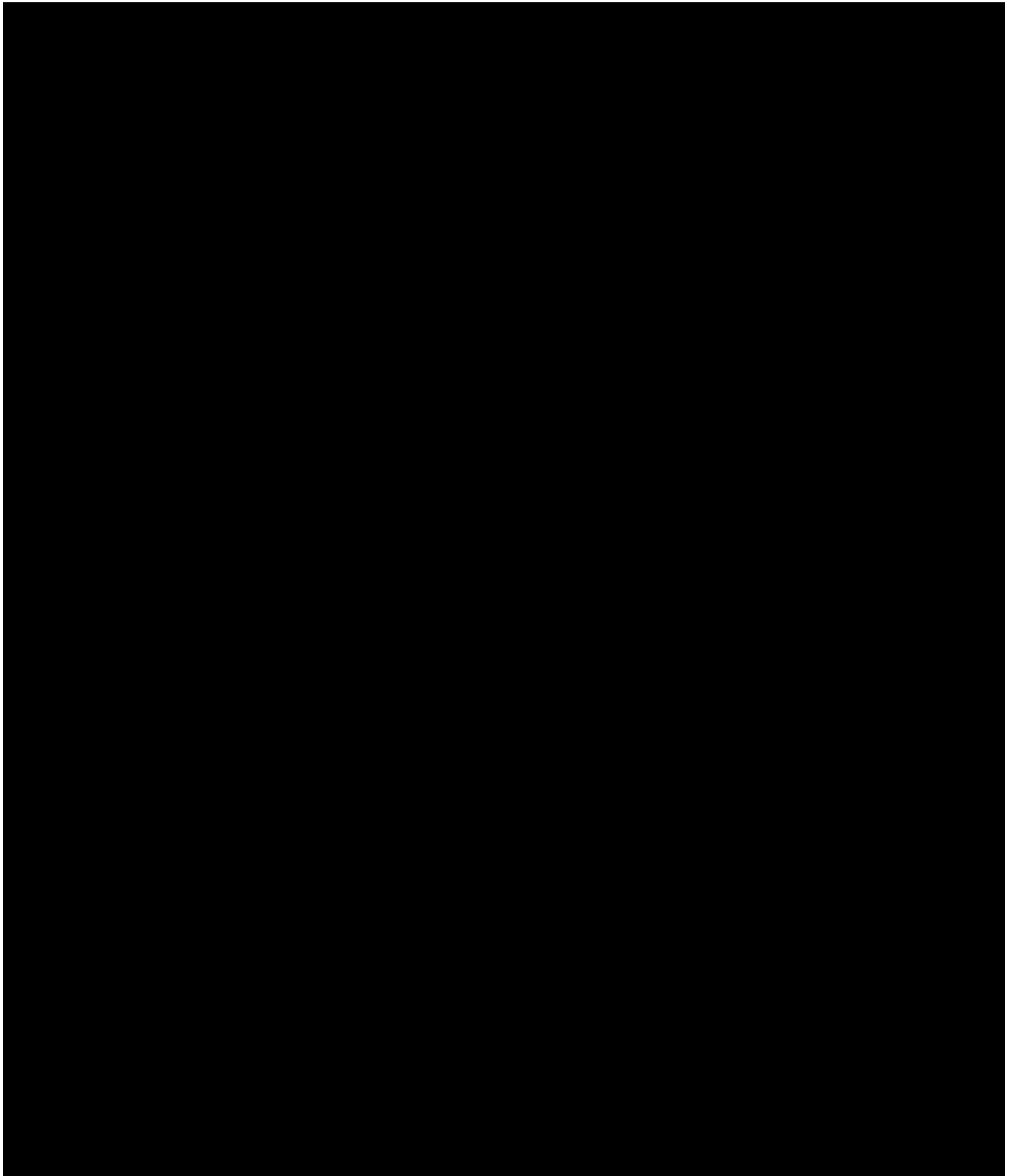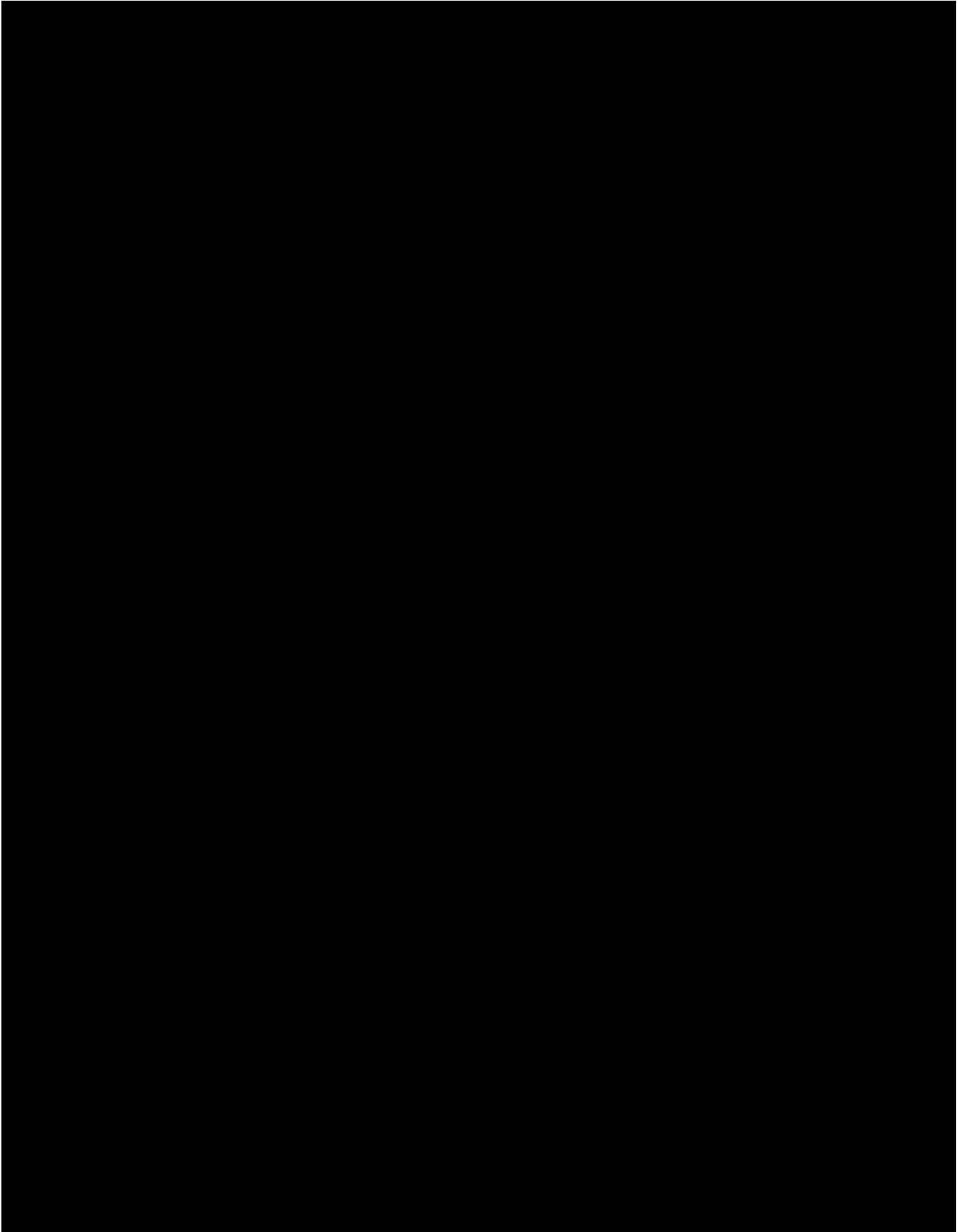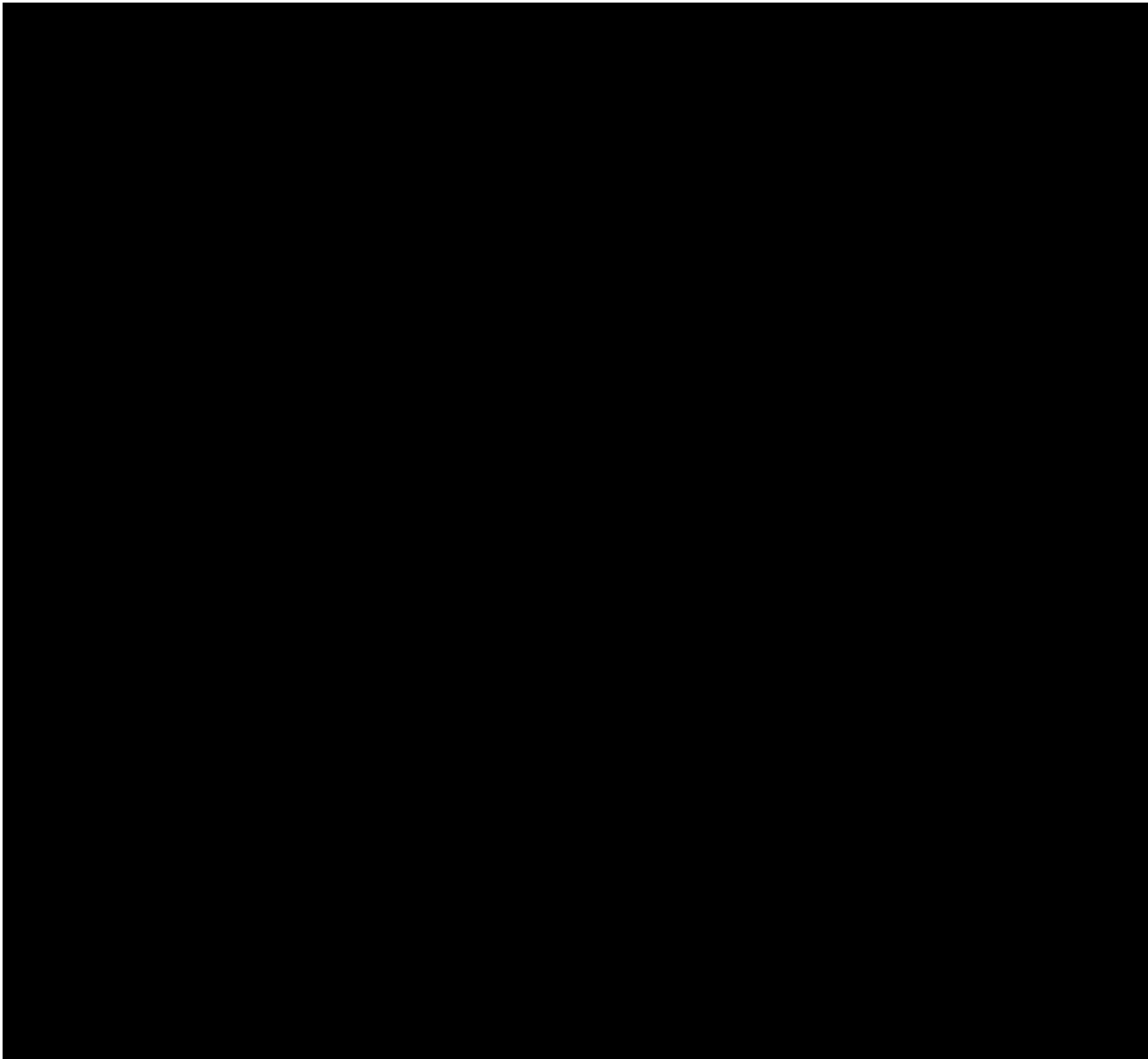
6   Sample Size and Power Calculations

The choice of sample size is not based on statistical considerations.

Approximately 56 subjects will be bilaterally implanted to obtain data for at least 50 subjects (100 eyes) at Month 6, assuming a dropout rate of 10% over a 6 month period. The precision estimates below are presented for individual eye summaries. All eye summaries will have increased precision.

For visual acuity, with a sample size of 50 eyes and assuming a standard deviation of 0.18 logMAR ███████████████████████████████ a two-sided 95%

confidence interval based on large sample z statistics will extend 0.05 logMAR from the observed mean.

For residual cylinder, a two-sided 95% confidence interval based on large sample z statistics will extend 0.11 D from the observed mean, assuming a standard deviation of 0.40 D ████

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For any event where a zero incidence is observed in 50 eyes implanted with study IOL, the upper exact binomial 95% confidence limit is less than 6%. Thus, with 95% confidence, the true adverse event rate is less than 6%.

7 References

None.

8 Revision History
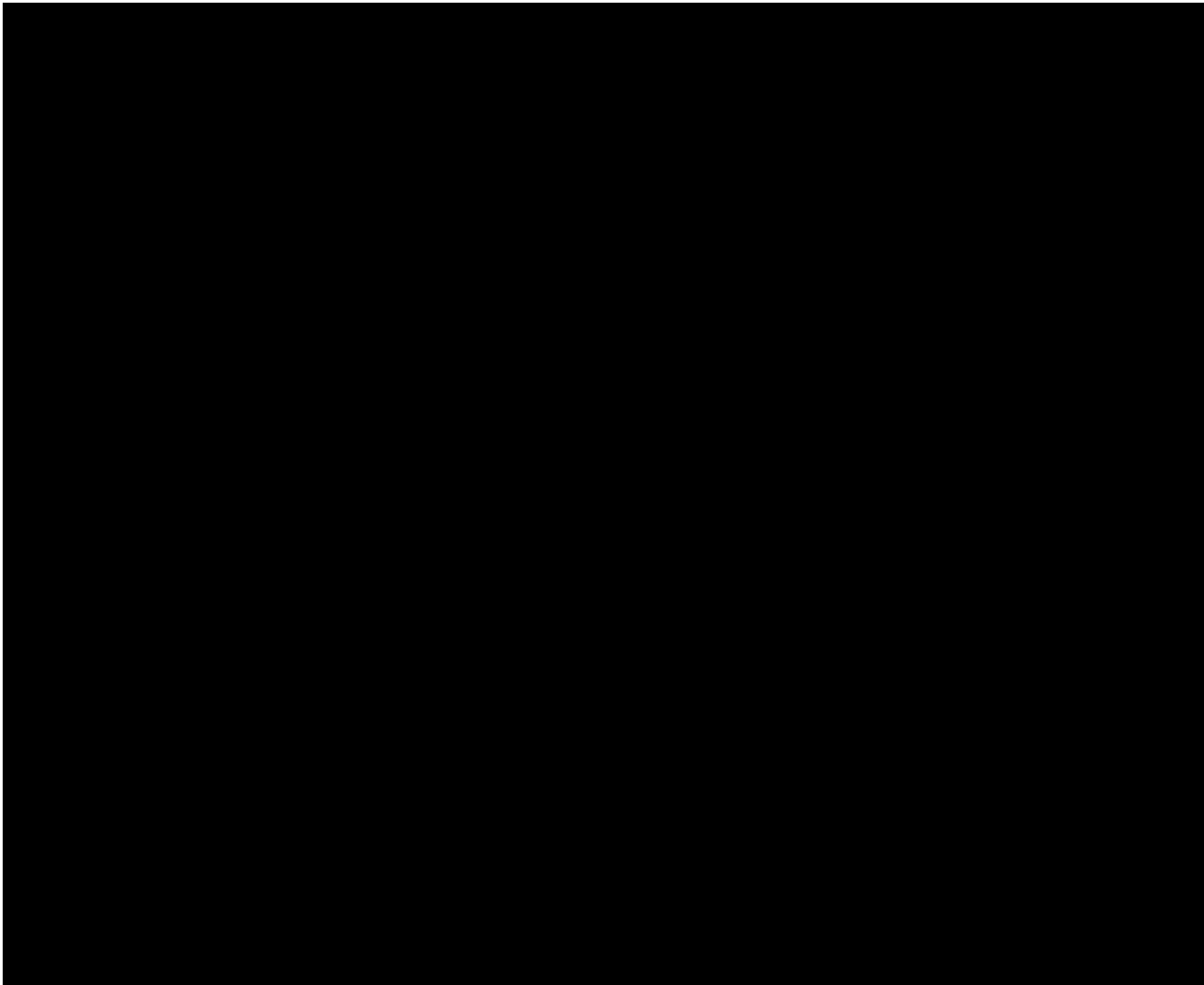
9   Appendix

Table 9-1   Schedule of Study Procedures and Assessments

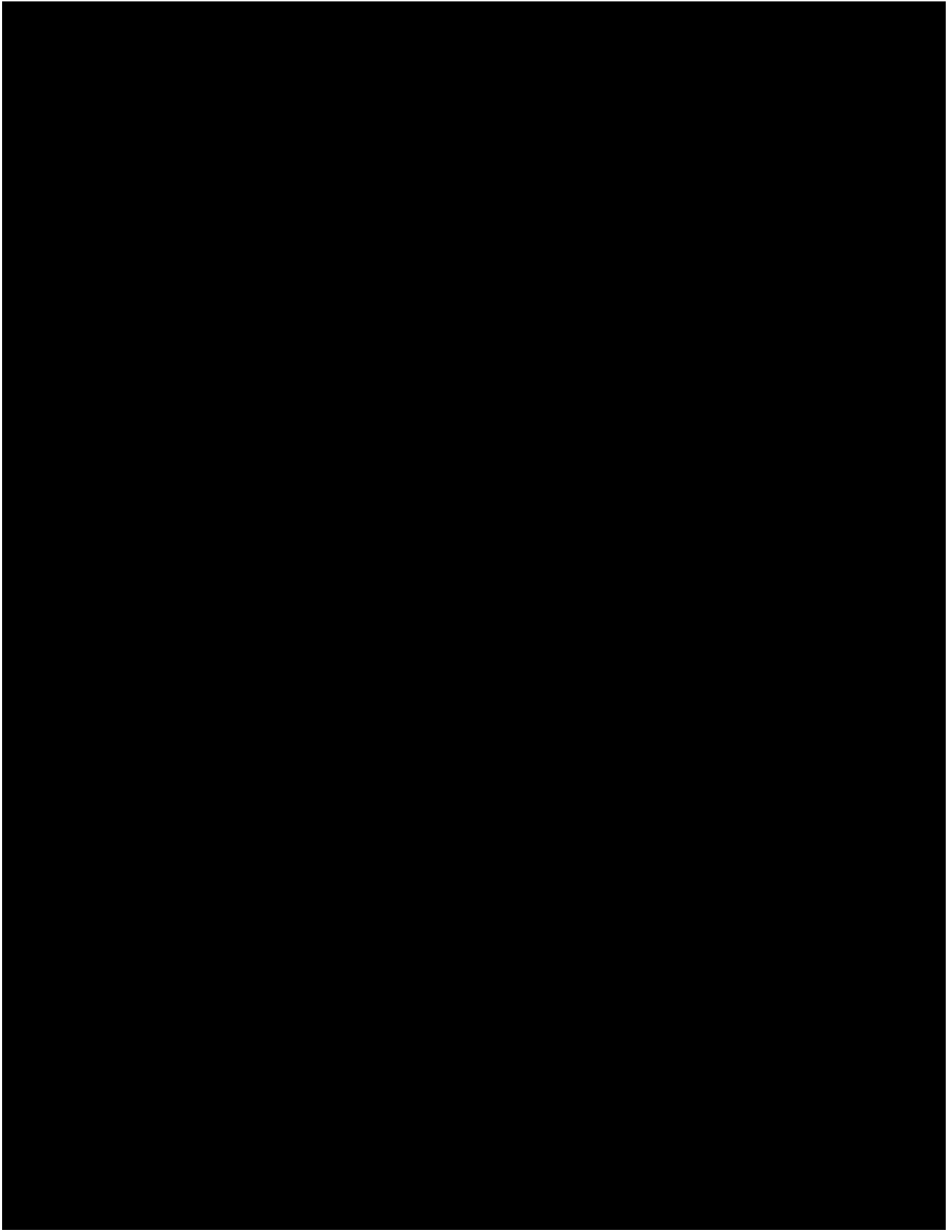|	Both Eyes	First Operative Eye			Second Operative Eye			Both Eyes		
	Visit 0 (Preop)	Visit 00 (Op)	Visit 1 Day 1 - 2	Visit 2 Day 7 - 14	Visit 00A (Op)*	Visit 1A Day 1 - 2	Visit 2A Day 7 - 14	Visit 3A Day[1] 30-60	Visit 4A Day[1] 90-120	Visit 5A Day[1] 180-210
Informed Consent	X									
Demographics	X									
Medical History[3]	X									
Concomitant Medications[3]	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[2]	X									
Inclusion/Exclusion	X	X			X					
Ocular Biometry (Axial Length, Keratometry, Anterior Chamber Depth with corneal thickness, lens thickness, white-to-white)	X									X
ALCON® Online Toric IOL Calculator (Barrett) (Intended Axis Placement)	X									
Actual axis of IOL orientation			X^1			X^2			X	X
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▬▬▬▬▬▬▬	■							■		
Target (Predicted) Residual Refractive Error (include spherical and cylinder)	X									
Administer Treatment(s)		X^1			X^2					
Operative Eye		X^1			X^2					
Surgical Problems		X^1			X^2					
Other Procedures at Surgery		X^1			X^2					
Incision Site		X^1			X^2					
Final Incision Size		X^1			X^2					
Lens Information		X^1			X^2					
IOL Damage		X^1			X^2					

		Both Eyes	First Operative Eye			Second Operative Eye			Both Eyes		
		Visit 0 (Preop)	Visit 00 (Op)	Visit 1 Day 1 - 2	Visit 2 Day 7 - 14	Visit 00A (Op)*	Visit 1A Day 1 - 2	Visit 2A Day 7 - 14	Visit 3A Day[1] 30-60	Visit 4A Day[1] 90-120	Visit 5A Day[1] 180-210
Manifest Refraction		X			X[1]			X[2]	X	X	X
Distance Visual Acuity (4 m) in photopic condition		■		■	■		■	■	■	■ ■	■ ■
	Best Corrected	■			■			■	■	■ X[b]	■ X[b]
▬▬▬▬	▬									■ ■	■ ■
▬▬▬	▬▬										
Intermediate Visual Acuity (60 cm) in photopic condition									■	■ ■	■ ■
	Distance Corrected								■	■ X[b]	■ X[b]
Near Visual Acuity (40 cm) in photopic condition									■	■ ■	■ ■
	Distance Corrected								■	■ X[b]	■ X[b]
▬▬▬▬	▬▬									■ ■	■ ■
▬										■	■
Slit Lamp Examination		X		X[1]	X[1]		X[2]	X[2]	X	X	X
██											
Dilated Fundus Examination		X			X[1]			X[2]	X	X	X
▬▬▬▬▬		■								■	■
QUVID Subject Survey		X[b]								X[b]	X[b]
Secondary Surgical Interventions				X[1]	X[1]		X[2]	X[2]	X	X	X
▬▬▬▬			■	■	■	■	■	■	■	■	■
Adverse Events[5]		X	X	X	X	X	X	X	X	X	X

NOTE:
* IOL implantation in the second eye is recommended to occur within 7-14 days from first eye implantation.
X: The 1st operative eye and the 2nd operative eye (if applicable) separately
X[1]: Only the 1st operative eye

X^2: Only the 2nd operative eye (if there is a 2nd operative eye)

X^b: Binocular examination (if there is a 2nd operative eye)

[1] Based on the 2nd eye post-operative surgery date (Visit 00A)

[2] In women of child bearing potential only

[3] Refer to Section 9.6 and Section 9.6, eCRF Guidelines, and MOP for collection and documentation requirements. Concomitant medications and medical history must be fully documented in the subject source documents. eCRF data will be Targeted:

      •Medical History: All ocular history, targeted systemic history*

      •Concomitant Medications: All ocular medications, targeted systemic medications

      *Pre-populated dropdown field