Next Generation Cataract and Vitreoretinal Surgery Study

STUDY ID

CTV678-E001

PROTOCOL

NCT06165744

Device Protocol for CTV678-E001
Title: Next Generation Cataract and Vitreoretinal Surgery Study

Protocol Number:	CTV678-E001
Clinical Investigation Type:	Traditional Feasibility
Test Product:	UNITY™ Vitreoretinal Cataract System (VCS)
Sponsor Name and Address:	Alcon Research, LLC, and its affiliates (“Alcon”) 6201 South Freeway Fort Worth, Texas 76134-2099

Investigator Agreement:

- I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices; applicable international and national regulations, laws, guidelines, and standards; the conditions of approval imposed by the reviewing IRB or regulatory authority; and in accordance with the ethical medical research principles outlined in the Declaration of Helsinki.
- I will supervise all testing of the device involving human subjects and ensure that the requirements relating to obtaining informed consent and IRB review and approval are met in accordance with applicable local and governmental regulations.
- I have read and understand the appropriate use of the investigational product(s) as described in the protocol, current investigator's brochure, product information, or other sources provided by the sponsor.
- I understand the potential risks and side effects of the investigational product(s).
- I agree to maintain adequate and accurate records in accordance with government regulations and to make those records available for inspection.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements of the sponsor and government agencies.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.

Have you ever been disqualified as an investigator by any Regulatory Authority? ☐ No ☐Yes
Have you ever been involved in a study or other research that was terminated? ☐ No ☐Yes If yes, please explain here:

Principal investigator:

Signature Date

Name and professional position:

Address:

Phone Number:

Off-hours Emergency Phone Number:

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[redacted]

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1 GLOSSARY OF TERMS

Names of Test Product(s)	Throughout this document, test product(s) will be referred to as the UNITY Vitreoretinal Cataract System (VCS).
Name of Comparator Product(s)	N/A
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device or comparator. *Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse.*
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device or comparator and whether anticipated or unanticipated. *Note: For subjects, this definition includes events related to the investigational medical device, comparator, or the procedures involved. For users or other persons, this definition is restricted to the use of the investigational medical device or comparator.* Requirements for reporting adverse events in the study can be found in Section 11.
Anticipated Serious Adverse Device Effect (ASADE)	An effect which by its nature, incidence, severity, or outcome has been identified in the risk assessment.
Clinical Investigation Plan (CIP)	The document(s) stating the rationale, objectives, design, and prespecified analysis, methodology, organization, monitoring, conduct, and record-keeping of the clinical

	investigation. *Note: The protocol and other documents referenced in the protocol (for example, the statistical analysis plan, the manual of procedures, the deviations and evaluability plan, and the protocol monitoring plan) comprise the CIP.*
Clinical Investigation Report (CIR)/Clinical Study Report	The document describing the design, execution, statistical analysis, and results of a clinical investigation. The clinical investigation report is synonymous with the clinical study report.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling related to the investigational medical device or the comparator.* Requirements for reporting device deficiencies in the study can be found in Section 11.
Enrolled Subject	Any subject who signs an ICF for participation in the study.
Point of Enrollment	The time at which, following recruitment and before any clinical investigation-related procedures are undertaken, a subject signs and dates the informed consent form.
Interventional Clinical Trial	A pre- or postmarket clinical investigation where the assignment of a subject to a particular medical device is decided in advance by a clinical investigation plan, or diagnostic or monitoring procedures requested in the CIP are in addition to those available as normal clinical practice and burden the subject.
Investigational Product	A preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used as a test or comparator product in a clinical trial, including a product with a

	marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan (CIP), or investigator's brochure (IB).
Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: • Death. • A serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: a) a life-threatening illness or injury *Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, i.e., it does not include an event which hypothetically might have caused death had it occurred in a more severe form.* b) any potentially sight-threatening event or permanent impairment to a body structure or a body function including chronic diseases. c) inpatient hospitalization or prolonged hospitalization. d) a medical or surgical intervention to prevent a) or b). This includes any ocular secondary surgical

	intervention excluding posterior capsulotomy. e) any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, congenital abnormality or birth defect including physical or mental impairment. *Note: Planned hospitalization for a preexisting condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.* *Refer to Section 11 for additional SAEs.*
Serious Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users, or other persons, and that requires prompt remedial action for other subjects, users, or other persons. *Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.*
Study Start	The start of the study is considered to coincide with the enrollment of the first patient.
Study Completion	The completion of the study is considered to coincide with the study-level last subject last visit or the decision to terminate the trial, whichever is later.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the risk assessment.
Use Error	User action or lack of user action while using the medical device that leads to a different result than that intended by

	the manufacturer or expected by the user. *Note:* *a) Use error includes the inability of the user to complete a task.* *b) Use errors can result from a mismatch between the characteristics of the user, user interface, task, or use environment.* *c) Users might be aware or unaware that a use error has occurred.* *d) An unexpected physiological response of the patient is not by itself considered a use error.* e) *A malfunction of a medical device that causes an unexpected result is not considered a use error.*
Vulnerable Subject	An individual who is unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response.

2 LIST OF ACRONYMS AND ABBREVIATIONS

Table 2-1 List of Acronyms and Abbreviations Used in This Protocol

Abbreviation	Definition
ACD	Anterior chamber depth
ADE	Adverse device effect
AL	Axial length
AE	Adverse event
ASADE	Anticipated serious adverse device effect
AUS	Australia
BCDVA	Best corrected distance visual acuity
BSS	Balanced salt solution
C	Celsius
cc	Cubic centimeter
CDE	Cumulative dissipated energy
CFR	Code of Federal Regulations
CIP	Clinical investigation plan
CIR	Clinical investigation report
CRF	Case report form
cpm	Cycle per minute
CSR	Clinical study report
D	Diopter
ECCE	Extracapsular cataract extraction
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European union
EUREQUO	European Registry of Quality Outcomes for Cataract and Refractive Surgery
F	Fahrenheit
FLACS	Femtosecond laser-assisted cataract surgery
FMS	Fluid management system
Frag	Fragmentation
GA	Gauge
GCP	Good clinical practice
HP	Hand piece
I/A	Irrigation/aspiration
IB	Investigator’s brochure
ICF	Informed consent form
IEC	Independent ethics committee
IFC	Illuminated flex curve
IOL	Intraocular lens
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional review board

Abbreviation	Definition
ISO	International Organization for Standardization
mL	Milliliter
mm	millimeter
mmHg	Millimeters of Mercury
MDR	Medical device reporting
MOP	Manual of procedures
N/A	Not applicable
N	Number
Nd:YAG	Neodymium-doped yttrium aluminum garnet
PCO	Posterior capsule opacification
Phaco	Phacoemulsification
Preop	Preoperative
Postop	Postoperative
SADE	Serious adverse device effect
SAE	Serious adverse event
SICS	Small incision cataract surgery
SLE	Slit lamp examination
SOC	Standard of care
SOP	Standard operating procedure
SSI	Secondary surgical intervention
TASS	Toxic anterior segment syndrome
USA	United States of America
USADE	Unanticipated serious adverse device effect
USV	Unscheduled visit
VA	Visual acuity
VCS	Vitreoretinal Cataract System
VFC	Viscous Fluid Control
WHO	World Health Organization

3 PROTOCOL SUMMARY

Investigational product type	Device
Study type	Interventional, traditional feasibility
Investigational products	UNITY VCS consisting of: 1. Console including remote control and foot controller 2. UNITY Anterior Vitrectomy Kit 3. UNITY TOTAL PLUS Combined Procedure Pack 4. 25GA/27GA Entry System 5. High Performance Viscous Fluid Control Pack 6. 25GA/27GA TETRASPOT Multi-spot Laser Probe 7. 27GA Illuminated Flexible Curved Laser Probe 8. 27GA Chandelier 9. 22GA Ozil Frag Pack 10. Ozil Frag Handpiece For more details regarding IP, please see IB and MOP. Comparator Product: N/A
Purpose and Scientific Rationale for the Study	The purpose of this study is to obtain device-specific safety and performance clinical data to support marketability in Europe and to collect formal user feedback.
Brief Summary of the Protocol	This is a prospective, single arm, nonrandomized, multicenter study of adults with clinically documented diagnosis of vitreoretinal disease(s) with or without cataract and who meet the inclusion/exclusion criteria.
Objective(s)	The objective is to obtain device-specific safety and performance clinical data to support marketability in Europe and to collect formal user feedback.
Endpoint(s)	Primary Performance Endpoint • Percent of 'yes' responses to the binary question of: "Did UNITY VCS using vitreoretinal or combined surgical functionality perform per the intended use as defined in protocol Section 5.1?"

	Secondary Performance Endpoints • Total time in the eye • Achievement of anatomical success at 3 months postop • Change in BCDVA at 3 months postop when compared to preop Safety Endpoints • Ocular and nonocular AEs and SAEs • Device deficiencies • Secondary surgical interventions • Unplanned intraoperative procedures

[redacted]

Study Design	This is a prospective, single arm, nonrandomized, unmasked, multicenter study.
Subject population	Adults ≥ 18 years requiring posterior segment surgery in the operating room with or without simultaneous cataract surgery.

	Planned number of subjects enrolled/consented: Approximately 120 subject eyes (unilateral subjects) Planned number of completed subjects: Approximately 100 subject eyes (unilateral subjects)
Sites and Locations	Planned number of clinical sites: up to 8 sites Planned locations (initial list of locations, which may change during start up or conduct according to study needs): Australia and/or United States
Key inclusion criteria (See Section 8.1 for a complete list of inclusion criteria)	• Adults ≥ 18 years requiring posterior segment surgery in the operating room with or without simultaneous cataract surgery • Clear media except for cataract and vitreous hemorrhage • In simultaneous cataract and vitreoretinal surgery, eligible to undergo primary hydrophobic acrylic IOL implantation into the capsular bag • For those with planned simultaneous cataract and vitreoretinal surgery, keratometry of 41 to 46 D, anterior chamber depth of greater than 2.5 mm, and axial length of 22 to 28 mm
Key exclusion criteria (See Section 8.2 for a complete list of exclusion criteria)	• Previous vitrectomy in the operative eye aside from those requiring silicone oil removal • Neovascular or uncontrolled glaucoma (IOP > 21 mmHg despite maximally tolerated medications/surgical interventions) • Preoperative hypotony (< 6 mmHg) • Planned glaucoma or postoperative surgeries during study aside from silicone oil removal (e.g., corneal refractive surgery) • Laser-assisted lens fragmentation • Inadequate pupil dilation (< 6 mm) • Unpredictable cases that would severely confound the results of the study per investigator's clinical judgment (e.g., endophthalmitis, TASS, tumor, complex dislocated IOL, penetrating or severe ocular trauma such as globe rupture, zonular instability, pseudoexfoliation, use of systemic medications known to complicate surgery, Coat's disease, Vogt-Koyanagi-Harada disease, or Bechet's disease)

Data analysis and sample size justification	The primary analysis set for effectiveness outcomes will be the full analysis set. The full analysis set includes all eyes with successful completion of surgery. The safety analysis set will include all eyes with attempted use of the UNITY VCS (successful or aborted after contact with the eye) and will be used for the safety outcomes. Attempted use of the UNITY VCS is defined as any time the device makes contact with the eye. There will be no hypothesis testing for any study outcome. All study outcomes will be presented as data listings or with summary statistics that are appropriate to the scale of the endpoint (continuous, dichotomous, etc.). Based on a sample of 100 surgeries, the expected half-width of the 95% confidence interval for the percentage of surgeons reporting 'yes' to the question "***Did UNITY VCS using vitreoretinal or combined surgical functionality perform per the intended use as defined in protocol Section 5.1?***" will be $1.96 \cdot \sqrt{(p(1-p)/100}$. This half-width is widest at p = 50%. Under this conservative assumption, the expected half-width is < 10% given the sample size of 100. Allow enrolment for an additional 10% for screen failure and 10% for loss to follow-up to ensure 100 completed subjects.

[redacted]

Table 3-1 Schedule of Study Procedures and Assessments

	Nominal Time ± Window Limits							
	Visit 0 (Screening)	**Visit 00 (Operative)**	**Visit 1 (1 Day)**	**Visit 2 (1 week)**	**Visit 3 (1 month)**	**Visit 4/Exit (3 month)**	**Early Exit[3]**	**Unscheduled Visit[3]**
Procedure/ Assessment	**Day -30 to 0**	**Day 0**	**Day 1 + 2 Days**	**Day 7 ± 3 Days**	**Day 30 ± 14 Days**	**Day 90 ±14 Days**	**N/A**	**N/A**
Eye	Both eyes	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye
Informed Consent	X							
Demographics	X							
Medical History	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X							
Urine Pregnancy Test[2]	X							
Dilated Pupil Size	X							
Keratometry*	X							
Biometry (ACD, AL)*	X							
Slit lamp exam	X		X	X	X	X	X	
Monocular BCDVA Using Snellen chart[c]	X		X [a]	X [a]	X	X	X	
IOP	X		X	X	X	X	X	
Dilated Fundus Exam	X		X [b]	X	X	X	X	
Total time in eye		X						

[redacted]

	Nominal Time ± Window Limits							
	Visit 0 (Screening)	**Visit 00 (Operative)**	**Visit 1 (1 Day)**	**Visit 2 (1 week)**	**Visit 3 (1 month)**	**Visit 4/Exit (3 month)**	**Early Exit[3]**	**Unscheduled Visit [3]**
Procedure/ Assessment	**Day -30 to 0**	**Day 0**	**Day 1 + 2 Days**	**Day 7 ± 3 Days**	**Day 30 ± 14 Days**	**Day 90 ±14 Days**	**N/A**	**N/A**
Eye	Both eyes	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye
[redacted]								
User Questionnaire		X						
Adverse Events	X	X	X	X	X	X	X	X
Device Deficiencies		X						

[redacted]

[2] Women of child-bearing potential only

[3] Unscheduled/Early Exit Visit – additional study assessments may be performed per investigator's discretion

[redacted]

[a] Visual acuity (VA) to be conducted per site's standard of care using Snellen chart

[redacted]

[c] BCDVA is done using manifest refraction

*As applicable

4 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments must be created by the study sponsor and must be approved by the IRB/IEC and global and regional health authorities, as applicable, prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all subjects currently enrolled in the study must sign the approved, revised informed consent (re-consent), as required by the IRB/IEC.

[redacted]

5 INTRODUCTION

5.1 Rationale and Background

To meet the demands of increasing number of cataract and vitreoretinal surgeries coupled with high patient expectations, ophthalmic surgeons desire the safest and most efficient device to remove the crystalline lens and complete vitreoretinal surgeries. The investigational device was developed to meet these needs by improving occlusion break surge responses, supporting smaller incision vitreoretinal surgeries, increasing vitrectomy cut speed, reducing scleral insertion force, improving instrument entry and tissue visualization while providing greater flow and IOP control as well as reducing phaco time and energy.

The intended purpose of UNITY VCS, in general, is to facilitate management of fluid and gases, as well as removal, grasping, cutting, illumination, and coagulation of ocular materials. The target patient population for this study are those undergoing vitreoretinal surgery with or without simultaneous cataract surgery.

Modern cataract procedures usually involve the use of an ultrasonic device that breaks up the crystalline lens (often cloudy) into small pieces, which are then gently removed from the eye with suction; this procedure is called phacoemulsification. Standard extracapsular cataract extraction (ECCE) and manual small incision cataract surgery (SICS) are other surgical methods that remove the cataract without an ultrasonic device. Phacoemulsification, or "phaco", is the surgical technique most often employed based on the European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) (Lundström 2012). Phacoemulsification is also the SOC based on guidelines from the American Academy of Ophthalmology (AAO 2016). Femtosecond laser-assisted cataract surgery (FLACS) uses a

femtosecond laser to create incisions, capsulotomies, and/or fragmentation patterns where only the laser fragmentation step assists in breaking up the cloudy lens into small pieces before removal, but the phacoemulsification machine would still be required to remove the lens. Vitreoretinal surgery had its beginnings in the 1970's and has been improved with many technological advancements that make it a more predictable, safe, and effective procedure (Ribeiro 2022). Modern vitreoretinal surgeries performed in the operative room involve vitrectomy and subsequent interventions as needed per the presenting patient condition including, but not limited to, epiretinal membrane, macular hole, vitreous hemorrhage, floaters, dislocated lens, retinal detachment, and diabetic retinopathy. Vitrectomy involves the removal of the vitreous humor while replacing it with BSS. Depending on the patient condition, tamponades such as air, gas, or other viscous fluid may also be used after the vitrectomy. An intraocular light source is always needed for visualization of the posterior segment of the eye. Abnormal tissue including tractional fibrous bands can be grasped, cut, and released. Coagulation is often employed under different situations; diathermy is used to stop bleeding while photocoagulation is used to reduce retinal detachment or formation of new retinal blood vessels. Combined or sequential vitreoretinal and cataract surgery can be performed and the decision is often based on multiple factors such as cost, convenience, and outcomes (Daud 2023). The intended clinical benefit of UNITY VCS is to aid in the execution of anterior and posterior segment ophthalmic surgery.

According to the World Health Organization (WHO), cataract is one of the leading causes of visual impairment and blindness, impacting 94 million globally (WHO 2022). Visual impairment is expected to continue to increase due to population growth and aging (WHO 2022). Cataract surgery is the only way to treat cataracts (NEI 2023). The most commonly performed ophthalmic procedure is cataract surgery (AAO 2023). While vitreoretinal surgery is less common than cataract surgery, surgical intervention is important in treating otherwise vision threatening posterior segment conditions. With improving diagnostics, an aging population and advances in ophthalmic surgical technology, the rate of patients requiring vitreoretinal surgeries is greatly increasing with one large study noting a 31% increase over approximately a decade (Wubben 2016). The advances in ophthalmic surgical technology in specific has been a big contributor to the increase in predictability of these procedures (Ribeiro 2022). As such, this study is relevant as it aims to enhance equipment used to perform cataract and vitreoretinal surgery with the potential to benefit a very large patient population globally.

Available alternative treatment options to UNITY VCS include other phacoemulsification and vitreoretinal systems. Cataract surgery is either performed manually or with a phacoemulsification system where only the latter uses ultrasound energy. Phacoemulsification is considered standard of care (AAO 2016) and is the preferred surgical technique in the majority of cases (Lundström 2012). While other interventions, such intravitreal injections, may be utilized, vitreoretinal surgery in the form of pars plana vitrectomy using a vitreoretinal machine remains a necessary step for many vitreoretinal conditions (Omari 2023).

The CENTURION and CONSTELLATION Vision Systems, the predecessors to UNITY VCS, are the most utilized anterior and posterior segment ophthalmic surgical systems in the world (2022 Cataract Surgical Equipment Market Report and 2023 Retinal Surgical Device Market Report). The CENTURION Vision System is Alcon's premium phacoemulsification system launched in 2013, with the addition of Active Sentry in 2019. The CONSTELLATION Vision System is Alcon's combined cataract and vitreoretinal system first launched in 2008 with many technological advancements made throughout its history with most notable being IOP control in 2009 and 20K cuts per minute with HYPERVIT probe added in 2019. The UNITY VCS was designed to improve upon the latest iteration of the CENTURION and CONSTELLATION Vision Systems currently used successfully in the market. As such, the UNITY VCS is intended to provide greater benefits than the current standard of care.

5.2 Purpose of the Study

The study aims to:

(1) Obtain device-specific safety and performance clinical data to support marketability in Europe

(2) Collect formal user feedback

At the end of the study, a clinical study report and lay summary, if applicable, will be prepared in accordance with applicable regulatory requirements and standards. The informed consent will specify that a lay summary, if applicable, will be made available after the study is completed.

There are no immediate plans to submit the results of this traditional feasibility study for publication; however, the results may be offered for publication if they are of scientific interest, or if the results relate to a product that is subsequently approved or cleared for marketing. Alcon reserves the right of prior review of any publication or presentation of information related to the study. The author(s) of the publication will be the individual with substantial contribution to the conception or design of the work, OR the acquisition, analysis,

or interpretation of data. Additionally, the author will draft the work or revise it critically for important intellectual content; provide final approval of the version to be published; and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

5.3 Risks and Benefits

The intended clinical benefit of UNITY VCS is to aid in the execution of anterior and posterior segment ophthalmic surgery which include the removal of the opacified, cloudy crystalline lens and to manage vitreoretinal disease. In comparison with predecessor systems, the UNITY VCS provides enhancements that are designed to benefit patients. The UNITY VCS has many enhancements in key areas including fluidics, energy delivery, higher vitrectomy cut speed and allowing greater use of higher gauge sizes. Use of higher gauge sizes may reduce time to close incision, lower surgically induced astigmatism, provide quicker VA improvements, less change in IOP, decreased hypotony, and less need for sutures ([redacted] Lubiński 2020, and Saleh 2020). UNITY VCS innovations have made design enhancements to the illumination output, viscous fluid control as well as vitrectomy and laser probes to overcome some of the reduction in efficiency currently observed with smaller gauge vitreoretinal surgery (Lee 2023). Higher vitrectomy cut speed in both clinical and simulated settings may improve safety by reducing retinal traction and improve efficiency due to greater aspiration flow (Doi 2023, Steel 2022). The fluidics enhancement was designed with the intent to allow improved control of flow for vitreous cutting and surgeons to operate at lower IOP and higher vacuum while maintaining chamber stability. In specific, operating at lower, more physiological IOP may be associated with greater reported patient comfort during surgery (Hou 2012), improved visual recovery due to better preservation of corneal endothelial health, and less macular edema postoperatively (Suzuki 2009, Chen 2012) as well as reduced complications due to less impact on retinal blood flow/reduction of ischemia (Findl 1997, Takhtaev 2019). The ultrasound energy enhancement was designed to improve crystalline lens cutting efficiency and reduce energy. The overall potential benefit would be a safer and more efficient procedure.

The clinical investigation process risks are managed through appropriate training and monitoring according to the protocol-specific monitoring plan. [redacted]

Complications may occur on the surgery day or throughout the postop period. As with any type of intraocular surgery, there is a possibility of complications due to anesthesia, drug reactions, and/or surgical problems. The surgical procedure can exacerbate a preexisting ocular condition

and can also lead to potential procedure related postop adverse events. [redacted]

[redacted]

[redacted]

In addition, a secondary surgical intervention (SSI) may be required following the initial surgery. SSIs include, but are not limited to vitreous aspirations, iridectomy for pupillary block, wound leak repair, intracameral and intravitreal antibiotic injections, additional posterior segment surgery including retinal detachment repair, and pars plana vitrectomy.

All the above-mentioned complications, adverse events, SSIs, and postoperative reported events have been reported because of the ophthalmic surgical procedures with use of a combined anterior and posterior segment surgical system. The UNITY VCS, the investigational device, is not expected to increase any harms or the likelihood of those harms when compared to predecessor devices. [redacted]. Any risk to subjects in this clinical study will be minimized by compliance with the eligibility criteria and study procedures, and by clinical oversight and monitoring.

The UNITY VCS is expected to provide greater benefits and no additional harms or likelihood of harms when compared to the widely and successfully marketed predecessor devices, the CENTURION and CONSTELLATION Vision Systems. As such, the expected benefits of using the UNITY VCS anterior and posterior segment functions are expected to outweigh the risks of ADEs for subjects that qualify for cataract surgery in this study.

Refer to the IB for additional information.

6 STUDY OBJECTIVES

6.1 Primary Objective(s)

Table 6-1 Primary Objective(s)

Objective(s)	Endpoint(s)
Performance: To obtain device-specific performance clinical data and to collect user feedback	***Primary Performance Endpoint:*** Percent of 'yes' responses to the binary question of: "Did UNITY VCS using vitreoretinal or combined surgical functionality perform per the intended use as defined in protocol Section 5.1?" ***Secondary Performance Endpoints:*** 1. Total time in the eye From first entry into eye/first trocar in, to incision closure/last trocar out 2. Achievement of anatomical success at 3 months postop Percent of 'yes' responses to the question "Was anatomical success achieved for intended treatment (ex: macular hole closure, retinal attachment, etc. as applicable for the patient's condition)?" 3. Change in BCDVA at 3 months postop when compared to preop

6.2 Secondary Objective(s)

Not Applicable

[redacted]

6.4 Safety Objective(s)

Table 6-2 Safety Objective(s)

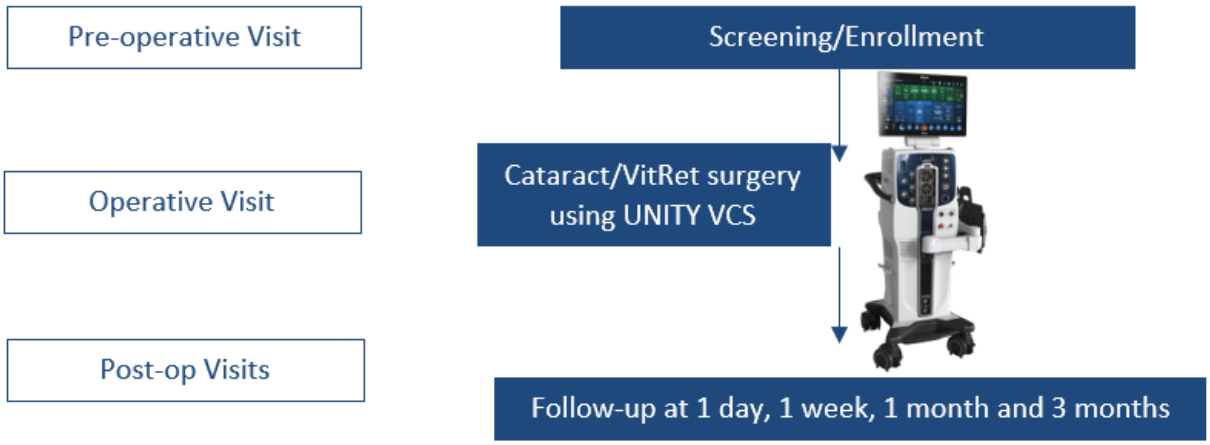
Objective(s)	Endpoint(s)
To obtain device-specific safety clinical data	• Ocular and nonocular AEs and SAEs • Device deficiencies • Secondary surgical interventions • Unplanned intraoperative procedures

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a prospective, single arm, nonrandomized and multicenter clinical study in Australia (AUS) and/or the United States of America (USA) with approximately a 3-month follow-up.

Figure 7-1 Study Design Flow



7.2 Rationale for Study Design

The UNITY VCS is a Class IIb nonimplantable medical device in the EU and AUS and a Class II nonimplantable medical device in the USA. For this class category, there are no currently well-established study designs governed by health authorities or international standards. The prospective design of this traditional feasibility study will reduce sources of bias and confounding variables. The intended patient population represents the majority of patients that will require use of the investigational device for posterior segment surgery in the operating

room with or without simultaneous cataract surgery. The inclusion/exclusion criteria were carefully selected to reduce the likelihood of severely confounding the study outcomes.

The study design was also carefully thought out to allow it to represent a real world setting to ensure minimal intervention to the site's standard of care; this ensures the study gains the most realistic response regarding device performance and safety. [redacted]

A potential weakness of the current study design is the fact that it is a single arm study. However, this single arm design is justified given that there are well established data regarding safety and performance of vitreoretinal surgery as well as combined vitreoretinal and cataract surgery. As such, the safety and performance results from this study can be compared against this rich body of evidence to ensure the device meets state of the art standards.

7.2.1 Purpose and Timing of Interim Analyses and Resulting Design Adaptations

Not applicable. There are currently no planned interim analyses.

7.3 Rationale for Duration of Treatment/Follow-up

The follow-up schedule was designed to allow collection of data at key time points that yield relevant performance and safety outcomes. The follow-up period will allow for adequate safety monitoring of adverse events; if patients develop complications, those will typically be present within approximately 1 month of cataract surgery and 3-months of vitreoretinal surgery.

7.4 Rationale for Choice of Comparator Product

There is no comparator in this study due to the nature of the study being a feasibility study.

7.5 Data Monitoring Committee

Not applicable

8 STUDY POPULATION

The study population will consist of male and female subjects (18 years or older) requiring posterior segment surgery in the operating room with or without simultaneous cataract surgery (unilaterally). It is aimed to enroll (consent) approximately 120 subjects in up to 8 sites in AUS and/or the USA with a target of 100 subjects treated, with approximately 10 to 40 subjects per

site. Site-specific targets may vary based upon individual site capabilities and each site may include more than one surgeon. Estimated time needed to recruit subjects for the study is approximately 3 months; however, unanticipated circumstances may shorten or lengthen this time and would not require amendment of this protocol. Because a 10% screening failure rate is expected and 10% for loss to follow-up, approximately 120 subjects are expected to be enrolled to ensure 100 completed subjects.

8.1 Inclusion Criteria

Written informed consent must be obtained before any study specific assessment is performed. Upon signing informed consent, the subject is considered enrolled in the study.

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Subject must be able to understand and sign an IRB/IEC approved informed consent form.
2. Willing and able to attend all scheduled study visits as required per protocol.
3. Adults ≥ 18 years requiring posterior segment surgery in the operating room without or with simultaneous cataract surgery
4. Clear media except for cataract and vitreous hemorrhage
5. In simultaneous cataract and vitreoretinal surgery, eligible to undergo primary hydrophobic acrylic IOL implantation into the capsular bag
6. For those with planned simultaneous cataract and vitreoretinal surgery, keratometry of 41 to 46 D
7. For those with planned simultaneous cataract and vitreoretinal surgery, with following biometry, anterior chamber depth of greater than 2.5 mm, and axial length of 22 to 28 mm

8.2 Exclusion Criteria

Subjects fulfilling **any** of the following criteria are not eligible for participation in this study.

1. Women of childbearing potential, defined as all women who are physiologically capable of becoming pregnant and who are not postmenopausal for at least 1 year or are less than 6 weeks since sterilization, are excluded from participation if any of the following apply:
    a. they are currently pregnant,

b. have a positive urine pregnancy test result at Screening,

c. intend to become pregnant during the study period,

d. are breastfeeding.

Subjects who become pregnant during the study will not be discontinued; however, data will be excluded from the effectiveness analyses because pregnancy can alter refraction and visual acuity results.

2. Previous vitrectomy in the operative eye aside from those requiring silicone oil removal
3. Neovascular or uncontrolled glaucoma (IOP > 21 mmHg despite maximally tolerated medications/surgical interventions
4. Preop hypotony (<6 mmHg)
5. Planned glaucoma or postoperative surgeries during study aside from silicone oil removal (e.g., corneal refractive surgery)
6. Laser-assisted lens fragmentation
7. Inadequate pupil dilation (< 6 mm)
8. Unpredictable cases that would severely confound the results of the study per investigator's clinical judgment (e.g., endophthalmitis, TASS, tumor, complex dislocated IOL, penetrating or severe ocular trauma such as globe rupture, zonular instability, pseudoexfoliation, use of systemic medications known to complicate surgery, Coat's disease, Vogt-Koyanagi-Harada disease, or Bechet's disease)
9. Currently participating in another drug or device clinical trial, or having participated in another drug or device clinical trial within 30 days of enrolment into this study

8.3 Rescreening of Subjects

Rescreening of subjects is not allowed in this study.

9 TREATMENTS ADMINISTERED

9.1 Investigational Product(s)

Test Product(s):	UNITY™ Vitreoretinal Cataract System (VCS)
Comparator Product(s) (If applicable):	Not applicable

Table 9-1 Test Product

Test Product:	UNITY VCS consisting of: 1. Console including remote control and foot controller 2. UNITY Anterior Vitrectomy Kit 3. UNITY TOTAL PLUS Combined Procedure Pack 4. 25GA/27GA Entry System 5. High Performance Viscous Fluid Control Pack 6. 25GA/27GA TETRASPOT Multi-spot Laser Probe 7. 27GA Illuminated Flexible Curved Laser Probe 8. 27GA Chandelier 9. 22GA Ozil Frag Pack 10. Ozil Frag Handpiece [redacted]
Manufacturer:	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, TX 76134 USA [redacted]
Indication for use and intended purpose in the current study:	Indications for Use The Unity VCS, consisting of the console and compatible devices, is indicated for use during anterior and posterior segment ophthalmic surgery. Intended Use The Unity VCS, consisting of the console and compatible devices, is intended to facilitate management of fluid and gases, as well as removal, grasping, cutting, illumination, and coagulation of ocular materials.
Product description and parameters available for this study:	The UNITY VCS in this study is a surgical instrument for use in anterior and posterior segment ophthalmic surgeries. The product's capabilities include driving a variety of surgical instruments that provide the ability to facilitate management of fluid and gases, as well as removal, grasping, cutting, illumination, and coagulation of ocular materials. Full product parameters are available for the current study.
Formulation:	N/A
Usage:	UNITY VCS will be used as directed in the user manual.
Packaging description:	Each UNITY VCS console and all compatible investigational devices will be packaged individually and have an investigational product specific serial or lot number.

[redacted]

Labeling description:	Investigational labeling regulations apply for:
	• UNITY VCS console
	  • Remote control
	  • Foot controller
	• UNITY Anterior Vitrectomy Kit
	• UNITY TOTAL PLUS Combined Procedure Pack
	• 25GA/27GA Entry System
	• High Performance Viscous Fluid Control Pack
	• 25GA/27GA TETRASPOT Multi-spot Laser Probe
	• 27GA Illuminated Flexible Curved Laser Probe
	• 27GA Chandelier
	• 22GA Ozil Frag Pack
	• Ozil Frag Handpiece
	
	These devices will be labeled appropriately (e.g., “CAUTION – Investigational device. Limited by Federal [or United States] law to investigational use” or “Exclusively for Clinical Investigation” or “For Clinical Trial Use Only”). Each unit will be identifiable via a serial or lot number.

Training and/or experience requirements for device:	UNITY VCS should only be used by ophthalmic surgeons and operating room staff. It should only be operated according to the operating instructions as listed in the associated manuals. [redacted]
Storage conditions:	Temperature and humidity apply to room environmental conditions preceding and during device use. Temperature: • 10 to 35°C (50 to 95°F) Operating • -10 to 55°C (14 to 131° F) Nonoperating

	Relative humidity: 10% to 95% without condensation See user manual for complete requirements and instructions.
Additional information:	Not applicable
Supply:	UNITY VCS and compatible devices will be shipped to the site by the sponsor. [redacted] Refer to the MOP for a detailed description.

More information on the test product can be found in the IB and directions for use for UNITY VCS.

[redacted]

9.3 Treatment Assignment/Randomization

Only after signing the ICF, a subject will be assigned a subject number by the electronic data capture system.

All subjects who meet the inclusion/exclusion criteria and sign informed consent will undergo posterior segment surgery in without or with simultaneous cataract surgery with the UNITY VCS. Bias will be minimized as this is a single arm study. If both eyes qualify for the study, the study eye will be determined per investigator's discretion.

There will be no randomization of subjects.

9.4 Treatment Masking

Not applicable as this is an open label, single arm study.

9.5 Accountability Procedures

Upon receipt of IPs, the investigator or delegate must conduct an inventory of equipment and accessories by serial or lot number, complete study-specific confirmation of receipt procedures as described in the MOP and retain any required documentation in the investigator's clinical study records.

Throughout the study, the investigator or delegate must maintain records of IP use for each subject. This record must be made available to the study monitor for the purposes of verifying the accounting of IP supplies. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation.

- All IPs sent to the investigator must be accounted for by study sponsor personnel, and in no case be used in an unauthorized manner.

- Refer to Section 11 for additional information on the reporting of device deficiencies and to the MOP for information on return of IPs associated with these events.

The investigator is responsible for allowing de-installation of the provided UNITY VCS console, return of all unused devices, and proper discarding of all used devices as directed. Please refer to MOP for additional details.

9.6 Changes to Concomitant Medications, Treatments/Procedures

After the subject is enrolled into the study, the investigator must instruct the subject to notify the study site about:

- Any new medications
- Alterations in dose or dose schedules for current medications,
- Any medical procedure or hospitalization that occurred or is planned
- Any nondrug therapies (including physical therapy and blood transfusions).

The investigator must document this information.

10 STUDY PROCEDURES AND ASSESSMENTS

Study assessments will be obtained prior to vitreoretinal with or without simultaneous cataract surgery with the UNITY VCS and postoperatively at the study visits outlined below:

- Screening – Visit 0 (Day -30 to 0 prior to treatment)
- Surgery – Visit 00 (Day 0)
- 1 Day – Visit 1 (Day 1 to 3)
- 1 Week – Visit 2 (Day 4 to 10)
- 1 Month – Visit 3 (Day 16 to 44)
- 3 Month/Exit – Visit 4 (Day 76 to 104)

In addition to the scheduled visits listed above, the following visit may apply as needed:

- USV (completed when a treated subject reports for additional follow-up)
- Early Termination Visit (when subject would like to withdraw from the study participation)

Clinical assessments to be obtained at study visits are outlined in Table 3-1 Schedule of Study Procedures and Assessments and are defined in the sections below.

10.1 Informed Consent and Screening

The investigator or delegate must explain the purpose and nature of the study and have the subject read, sign, and date the IRB/IEC-approved informed consent document. The subject must sign the ICF BEFORE any study-specific procedures or assessments can be performed, including study-specific screening procedures. Additionally, have the individual obtaining consent from the subject and a witness, if applicable, sign and date the informed consent document.

The investigator or delegate must provide a copy of the signed document to the subject and place the original signed document in the subject's chart, or provide documentation as required by local regulations.

If a patient has reported for routine vitrectomy and/or cataract screening, then data obtained from the routine evaluation can be used for screening data as long as protocol requirements for timeframe (within 30 days of surgery) and required details have been met. Routine vitreoretinal and/or cataract screening data include, but are not limited to SLE, IOP, dilated pupil size, keratometry, biometry (ACD, AL), Snellen BCDVA with manifest refraction, and dilated fundus exam.

10.2 Description of Study Procedures and Assessments

Study-specific procedures and assessments described here may include standard of care; other standard of care procedures performed in the clinical management of the subject are not excluded.

Detailed descriptions of assessments and procedures are provided in the MOP. The investigator is responsible for ensuring responsibilities for all procedures and assessments are delegated to appropriately qualified site personnel.

The enrollment on this study is competitive and once the target number of subjects is achieved, sponsor will close the enrollment.

10.2.1 Demographics

Obtain demographic information including age, race, ethnicity, and sex.

10.2.2 Medical and Ocular History

Collect medical history information, including information on all medications used within the past 30 days. Include herbal therapies, vitamins, and all over-the-counter as well as

prescription medications. Throughout the subject's participation, obtain information on any changes in medical health and/or the use of concomitant medications.

Medical history and concomitant medications will be collected in the eCRF as outlined in the MOP.

10.2.3 Adverse Event Collection: Safety Assessment

Assess and record any adverse events that are observed or reported since the previous visit, including those associated with changes in concomitant medication dosing.

Note: AEs and device deficiencies must be recorded for all enrolled subjects from the time of signature of informed consent, regardless of subject enrollment status (screen failure or randomized).

10.2.4 Slit Lamp Biomicroscopy: Safety Assessment

SLE of the cornea, iris/anterior chamber and lens must be performed before instillation of any diagnostic eye drops.

Refer to the MOP for grading scales for study specific assessments.

10.2.5 Device Deficiencies: Safety Assessment

Assess and record any device deficiencies that are reported or observed since the previous visit. Requirements for reporting device deficiencies in the study can be found in Section 11.

Note: AEs and device deficiencies must be recorded for all enrolled subjects from the time of signature of informed consent, regardless of subject enrollment status (screen failure).

10.2.6 Dilated Fundus: Safety Assessment

Dilated fundus examination includes ophthalmoscopic assessments of the vitreous, retina, macula, choroid, and optic nerve.

10.2.7 Best Corrected Distance Visual Acuity: Safety Assessment

Snellen visual acuity testing with manifest refraction must be performed prior to any assessment requiring administration of eye drops to dilate the eye, or any assessment requiring contact with the eye.

10.2.8 Intraocular Pressure: Safety Assessment

Intraocular pressure must be measured using SOC.

10.2.9 Urine Pregnancy Test: Other Assessment

A urine pregnancy test is required for female subjects of childbearing potential that are not postmenopausal or surgically sterile.

10.2.10 Keratometry: Eligibility Assessment

Capture keratometry measurements of the central cornea using SOC. This assessment is required only when subjects are undergoing cataract surgery.

10.2.11 Pupil Size: Eligibility Assessment

Measure dilated pupil size under photopic condition using SOC.

10.2.12 Biometry: Eligibility Assessment

Perform biometry using SOC. Document the following: ACD, AL. This assessment is required only when subjects are undergoing cataract surgery.

10.2.13 Total Time in the Eye: Secondary Performance Assessment

Obtain time from first entry into eye/first trocar into incision closure/last trocar out using a stopwatch.

10.3 Unscheduled Visits

An Unscheduled Visit (USV) is defined as follows:

- Ocular examination that is not SOC and not required by the protocol
- Examination conducted by the study staff
- New findings, or change to a previous finding was discovered

If a subject visit occurs between any regularly scheduled visit and the visit is conducted by study personnel, this visit must be documented as an Unscheduled Visit. If the subject seeks medical attention outside the clinic (for example, at an emergency room) or at the clinic but is seen by non-study personnel, the investigator is to capture adverse event-related information on the adverse event form upon becoming aware.

During all unscheduled visits, the investigator must conduct the following procedures:

- Collect adverse event information, if applicable
- Collect device deficiency information, if applicable
- Collect SSI information, if applicable
- Record changes in medical condition or concomitant medication

The investigator may perform additional procedures for proper diagnosis and treatment of the subject. These include but are not limited to those noted in Table 3-1 Schedule of Study Procedures and Assessments. The investigator must document this information in the subject's case history source documents.

If during a USV the subject is discontinuing from the study, the investigator must conduct Exit procedures according to Table 3-1 Schedule of Study Procedures and Assessments and Section 10.4.3, as possible.

10.4 Discontinued Subjects

10.4.1 Screen Failures

Subjects who were excluded from the study after signing the informed consent and prior to exposure to IP.

The investigator must document the reason for screen failure in the subject's case history source documents.

Subject numbers must not be reused.

10.4.2 Discontinuations

Discontinued subjects are individuals who voluntarily withdraw or are withdrawn from the study by the investigator after signing informed consent, meeting eligibility criteria, and are exposed to IP.

Subject numbers of discontinued subjects must not be reused (i.e., subject replacement is not allowed).

Subjects may discontinue from study or study treatment at any time for any reason. Subjects may also be discontinued from study treatment at any time if, in the opinion of the investigator, continued treatment poses a risk to their health.

For subjects choosing to discontinue from the study after exposure to IP, the investigator must complete all Exit procedures according to Table 3-1 Schedule of Study Procedures and Assessments, if the subject is willing and able, and if in the opinion of the investigator it is safe for the subject to do so.

The investigator must document the reason for study or treatment discontinuation in the subject's case history source documents.

To ensure the safety of all subjects who discontinue early, investigators must assess each subject and, if necessary, advise them of any therapies and/or medical procedures that may be needed to maintain their health.

10.4.3 Schedule of Procedures and Assessments for Subjects Discontinued from Investigational Product

If a subject discontinues from study treatment, every effort must be made to keep the subject in the study and to continue with the study assessments as specified in the schedule of study procedures and assessments until the final visit.

10.5 Clinical Study Termination

The study sponsor reserves the right to suspend or close the investigational site or suspend or terminate the study in its entirety at any time.

If the clinical study is prematurely terminated or suspended by the study sponsor:

- The study sponsor must:
    - Immediately notify the investigator(s) and subsequently provide instructions for study termination.
    - Inform the investigator and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension.
- The investigator must:
    - Promptly notify the IRB/IEC of the termination or suspension and of the reasons.
    - Provide subjects with recommendations for poststudy treatment options as needed.

The investigator may terminate the site's participation in the study for reasonable cause.

10.5.1 Follow-up of Subjects after Study Participation has Ended

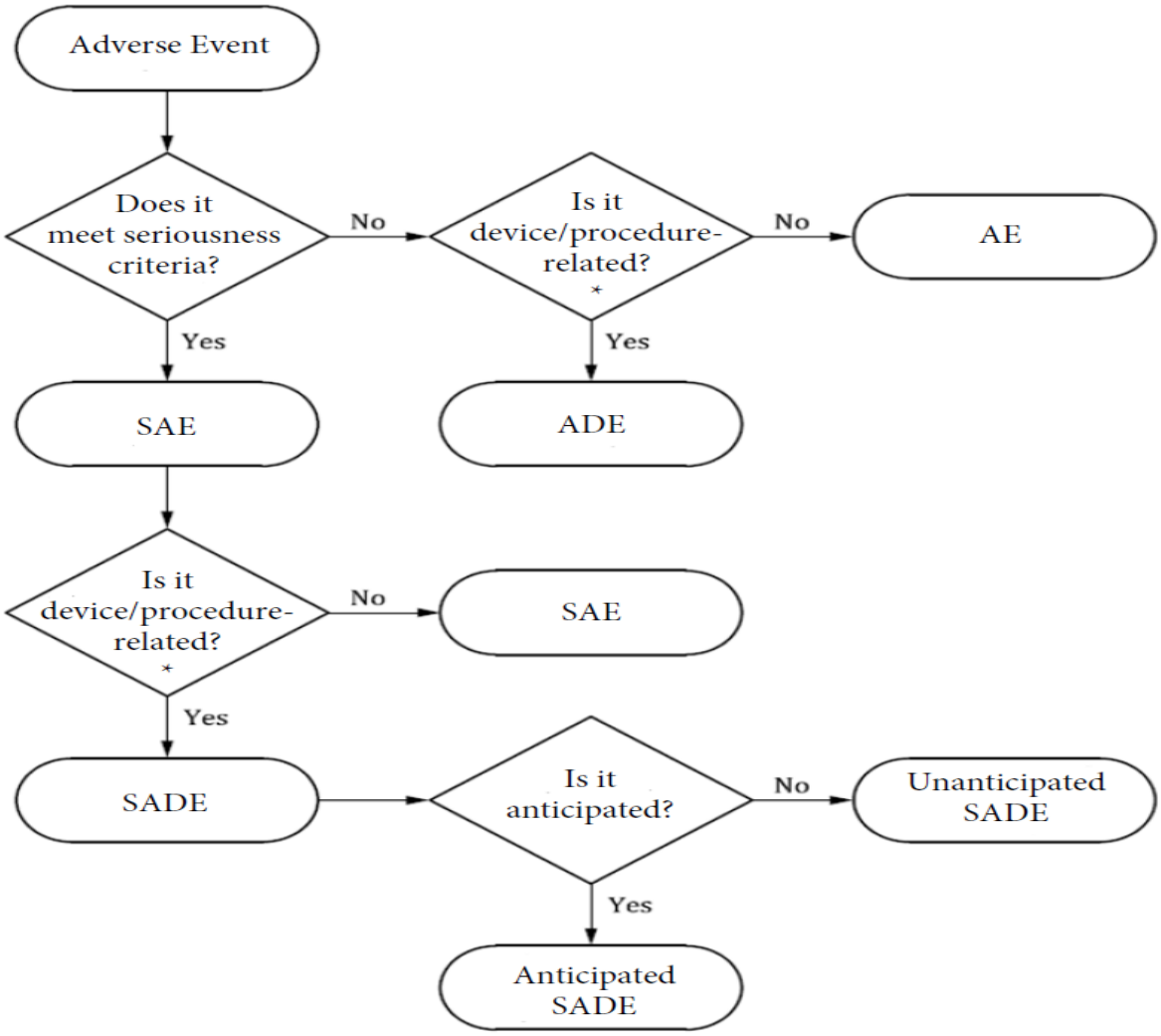
Following this study, the subject will return to their eye care professional for their routine eye care.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 General Information

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device (test product). Refer to the Glossary of Terms and figures below for categories of AEs and SAEs.

Figure 11-1 Categorization of All Adverse Events



*In this study, only AEs related to the IP/device (i.e., UNITY VCS) are considered as device related ADE.

Specific Events Relevant to this Protocol

In addition to reporting all AEs (serious and nonserious) meeting the definitions, the investigator must report any occurrence of the following as an SAE including but not limited to:

Serious Adverse Events

- Corneal incision site leakage
- Sclerotomy site leakage

- Toxic anterior segment syndrome
- Posterior capsular tear
- Vitreous prolapse
- Iridodialysis
- Iatrogenic retinal tear
- Chronic corneal edema (corneal stromal or epithelial swelling resulting in BCDVA of ≤ 20/40 at ≥ 1 month)
- Clinically significant cystoid macular edema
- Uncontrolled increase in IOP ≥ 10 mmHg over baseline and at least 25 mmHg
- Endophthalmitis
- Retinal detachment
- Retinal vascular occlusion
- Pupillary block
- Suprachoroidal hemorrhage
- Vitreous hemorrhage
- Secondary surgical intervention (excluding posterior capsulotomy, planned surgical intervention such as laser photocoagulation and silicone oil removal)

NOTE: Wound burps during the first week postoperatively, suture removal, planned surgical interventions such as blepharoplasty, laser photocoagulation, silicone oil removal, and Nd:YAG capsulotomy (for PCO) are not considered adverse events for this study.

AEs occurring in association with a device that is used in conjunction with the UNITY VCS (e.g. gas, and silicone oil) will be classified separately from those associated with the investigational device itself. Expected complications from use of femtosecond laser-assisted procedures as noted in Section 5.3 and additional medical interventions (e.g. ocular injections) will not be considered device related AEs.

In addition, aqueous cells and flare, corneal edema, eye redness, raised IOP, subconjunctival hemorrhage, and superficial punctate keratitis are examples of early postop findings that are typically observed following ocular surgery. These are not considered AEs if they can be reasonably expected to resolve within 2 weeks and not result in any untoward long term visual outcome impact.

Any other potentially sight-threatening event may also be considered serious based on the judgment of the investigator and should be reported appropriately as delineated in Section 11.3.

Device Deficiencies

A device deficiency may or may not be associated with subject harm (i.e., ADE or SADE); however, not all ADEs or SADEs are due to a device deficiency. The investigator should determine the applicable category for the identified or suspect device deficiency and report any patient harm separately. [redacted]

11.2 Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the standard questions shown below and report as applicable:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take because of a new health issue since your last study visit?"

In addition, changes in any protocol-specific parameters and/or questionnaires evaluated during the study are to be reviewed by the investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant, in the opinion of the investigator, is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

11.3 Procedures for Recording and Reporting

AEs are collected from the time of informed consent. Any preexisting medical conditions or signs/symptoms present in a subject prior to the start of the study (i.e., before informed consent

is signed) are not considered AEs in the study and should be recorded in the medical history section of the eCRF.

For each recorded event, the ADEs and SAEs documentation must include: date of occurrence, severity, treatment (if applicable), outcome, and assessments of the seriousness and causality. In addition, the investigator must document all device deficiencies reported or observed with the test product on the device deficiency eCRF. The site must submit all available information on ADEs, SAEs, and device deficiencies to the study sponsor immediately as follows:

- ADEs or SAEs are documented on the Serious Adverse Event and Adverse Device Effect eCRF within 24 hours of the investigator's or site's awareness.
- Device deficiencies are documented on the Device Deficiency eCRF within 24 hours of the investigator's or site's awareness.
- Additional relevant information after initial reporting must be entered into the eCRF as soon as the data become available.
- Document any changes to concomitant medications on the appropriate eCRFs.
- Document all relevant information from discharge summary, autopsy report, certificate of death etc., if applicable, in the narrative section of the Serious Adverse Event and Adverse Device Effect eCRF.

Note: Should the EDC system become nonoperational, the site must complete the appropriate paper serious adverse event and adverse device effect and/or device deficiency form. The completed form is emailed to the study sponsor at msus.safety@Alcon.com for USA-based sites and at Australia.auff-complaints@alcon.com for AUS-based sites, according to the timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.

In addition to recording all AEs into the EDC system, any AEs and device deficiencies for non-study marketed devices/products (e.g., Alcon's or other manufacturers' products used concomitantly during the study will be considered and processed as spontaneous following the post market vigilance procedures) and should be communicated to the device's/product's manufacturer as per local requirements.

Study sponsor representatives may be contacted for any protocol related question and their contact information is provided in the MOP that accompanies this protocol.

Further, depending upon the nature of the AE or device deficiency being reported, the study sponsor may request copies of applicable portions of the subject's medical records. The

investigator must also report all AEs and device deficiencies that could have led to a SADE according to the requirements of regulatory authorities or the IRB/IEC.

Intensity and Causality Assessments

Where appropriate, the investigator must assess the intensity (severity) of the AE based on medical judgment with consideration of any subjective symptom(s), as defined below:

Intensity (Severity)

Mild — An AE is mild if the subject is aware of but can easily tolerate the sign or symptom.

Moderate — An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.

Severe — An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

For every AE in the study, the investigator must assess the causality (related or not related to the medical device or study procedure). An assessment of causality will also be performed by study sponsor utilizing the same definitions, as shown below:

Causality

Related — An AE classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the medical device or study procedure has not been demonstrated, but there is a reasonable possibility that the AE was caused by the medical device or study procedure.

Not Related — An AE classified as not related may either be definitely unrelated or simply unlikely to be related (i.e., there are other more likely causes for the AE).

The study sponsor will assess the AEs and may upgrade the investigator's assessment of seriousness and/or causality. The study sponsor will notify the investigator of any AEs that are upgraded from nonserious to serious or from unrelated to related.

11.4 Return Product Analysis

Study sponsor representatives and their contact information are provided in the MOP that accompanies this protocol.

Alcon study products associated with device deficiencies and/or product related AEs should be returned and must include the complaint number which will be provided by study sponsor after the case is entered in the study sponsor's Global Product Complaint Management System (GPCMS).

11.5 Unmasking of the Study Treatment

Not applicable; this study is an open label study.

11.6 Follow-Up of Subjects with Adverse Events

The investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study.

The investigator should provide the study sponsor with any new safety information (which includes new AEs and changes to previously reported AEs) that may affect the safety evaluation of the device. For AEs that are unresolved/ongoing at time of discontinuation, any additional information received at follow-up should be documented in the eCRFs up to study completion (i.e., database lock). Any additional data received up to 6 months after a subject completed the study should be documented and available upon the study sponsor's request.

All complaints received after this time period will be considered and processed as spontaneous (following the post market vigilance procedures) and should be communicated to the medical device's manufacturer as per local requirements. The investigator should also report complaints on non-Alcon products directly to the manufacturer as per the manufacturer's instructions or local regulatory requirements.

11.7 Pregnancy in the Clinical Study

Pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case-by-case basis. An Alcon form will be utilized to capture all pregnancy-related information until birth of the child.

12 ANALYSIS PLAN

12.1 Subject Evaluability

Final subject evaluability must be determined prior to locking the database, based upon the deviations and evaluability plan.

12.2 Analysis Sets

All eligible subjects will be screened to determine if they meet all inclusion and no exclusion criteria. Subjects who provide informed consent will be considered enrolled in the study.

12.2.1 Full Analysis Set

The primary analysis set for the effectiveness outcomes will be the full analysis set. The full analysis set includes all eyes with successful completion of surgery.

12.2.2 Safety Analysis Set

The safety analysis set will include all eyes with attempted use of the UNITY VCS (successful or aborted after contact with the eye) and will be used for the safety outcomes. Attempted use of the UNITY VCS is defined as any time the device makes contact with the eye.

12.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for each subject. Counts and percentages will be presented for categorical variables such as sex, age, race, and ethnicity. Count (n), mean, standard deviation, median, minimum, and maximum will be presented for continuous variables such as age.

12.4 Effectiveness Analyses

12.4.1 Analysis of Primary Effectiveness Endpoint(s)

The primary performance endpoint is the percentage of surgeons reporting ‘yes’ to the binary question of: ***“Did UNITY VCS using vitreoretinal or combined surgical functionality perform per the intended use as defined in protocol Section 5.1?"***

12.4.1.1 Statistical Hypotheses

No hypothesis testing of the primary effectiveness endpoint(s) is planned.

12.4.1.2 Analysis Methods

After each surgery, the surgeon completes a user questionnaire. For subjects in the full analysis set, the rate of ‘yes’ responses to the question listed above will be presented with a count and percentage and will be accompanied by a two-sided exact binomial 95% confidence interval.

12.4.2 Analysis of Secondary Effectiveness Endpoints

The secondary endpoints are:

- Total time in the eye from first entry into eye/first trocar in, to incision closure/last trocar out
- Achievement of anatomical success at 3 months postop, i.e., percent of 'yes' responses to the question "Was anatomical success achieved for intended treatment (e.g., macular hole closure, retinal attachment, etc. as applicable for the patient's condition)?"
- Change in BCDVA at 3 months postop when compared to preop

12.4.2.1 Statistical Hypotheses

No hypothesis testing of the secondary effectiveness endpoint(s) is planned.

12.4.2.2 Analysis Methods

At the surgical visit, the total time in the eye will be recorded as the time from first entry into eye/first trocar in, to incision closure/last trocar out. The total time in eye will be summarized with the number of observations, mean, standard deviation, median, minimum, and maximum times in minutes. A listing will accompany this summary.

At the end of follow-up for each patient, surgeons will evaluate the success of the surgery. For subjects in the full analysis set, the rate of 'yes' responses to the question "was anatomical success achieved for intended treatment (e.g., macular hole closure, retinal attachment, etc. as applicable for the patient's condition)?" will be presented with a count and percentage and will be accompanied by a two-sided exact binomial 95% confidence interval.

BCDVA will be recorded in Snellen and collected at screening, 1 month, and 3 months. BCDVA will be converted to decimal VA. Observed decimal BCDVA values at each study visit and change from 3 months postoperative visit to screening value for the study eye will be presented descriptively (count, mean, median, standard deviation, minimum, and maximum). A categorical summary of Snellen values (not converted to decimal VA) will be produced and will include counts and percentages for each category at screening, 1 month, and 3 months. A listing will be provided which presents visual acuity results at each visit, including data from 1 day and 1 week visits, where uncorrected data may be recorded per standard of care.

12.5 Handling of Missing Data

No imputation of missing data is planned.

12.6 Safety Analyses

The safety endpoints are:

- Ocular and nonocular AEs and SAEs
- Device deficiencies
- Secondary surgical interventions
- Unplanned intraoperative procedures

There are no safety hypotheses planned in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events as well as the other listed parameters.

All adverse events occurring from the time a subject sign informed consent to study exit will be accounted for in the reporting. Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. Descriptive summaries (counts and percentages) and listings will be presented. Individual subject listings will be provided for AEs that occur after signing informed consent but prior to exposure to IP.

12.6.1 Analysis of Primary Safety Endpoint(s)

All adverse events reported to Alcon will be accounted for in the reporting. Descriptive summaries (counts and percentages) and listings will be presented. The applicable definition of an adverse event is in the study protocol. A listing of all adverse events will be constructed to provide further details.

The applicable definition of a device deficiency is in the study protocol. A frequency table showing counts for each device deficiency category will be presented. In addition, a listing of all device deficiencies will be provided.

Descriptive statistics (counts, percentages, and two-sided 95% exact binomial confidence intervals) of eyes with secondary surgical interventions (SSIs) will be presented. In addition, a listing of subjects with SSIs will be produced.

Unplanned intraoperative procedures that occur during surgery will be recorded. Descriptive statistics including the count, percentage, and a two-sided 95% exact binomial confidence interval for the percentage will be produced and will be accompanied by a listing.

12.7 Interim Analyses and Reporting

No interim analyses are planned.

12.8 Sample Size Justification

Based on a sample of 100 surgeries, the expected half-width of the 95% confidence interval for the percentage of surgeons reporting 'yes' to the question ***"Did UNITY VCS using vitreoretinal or combined surgical functionality perform per the intended use as defined in protocol Section 5.1?"*** will be $1.96 \cdot \sqrt{(p(1-p)/100)}$. This half-width is widest at p = 50%. Under this conservative assumption, the expected half-width is < 10% given the sample size of 100.

Allow enrollment for an additional 10% for screen failure and 10% for loss to follow-up to ensure 100 completed subjects.

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Subject Confidentiality

The investigator must ensure that the subject's identity is kept confidential throughout the course of the study. In particular, the investigator must keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study participant. The study sponsor may collect a copy of the enrollment log ***without any directly identifying subject information***.

The study sponsor may share patient-level data collected in this trial with qualified researchers to help facilitate product development or enhancements in research that is not directly related to the study objectives. The informed consent explains this to the study subject.

13.2 Completion of Source Documents and Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the CRFs exist and are accessible for verification by the site monitor, and all discrepancies shall be appropriately documented via the query resolution process. Site monitors are appointed by the study sponsor and are independent of study site staff.

If electronic records are maintained, the method of verification must be determined in advance of starting the study.

At a minimum, source documents include the following information for each subject:

- Subject identification (name, sex, race/ethnicity)

- Documentation of subject eligibility
- Date of informed consent
- Dates of visits
- Documentation that protocol specific procedures were performed
- Results of study parameters, as required by the protocol
- IP accountability records
- Documentation of AEs and other safety parameters (if applicable)
- Records regarding medical histories and the use of concomitant therapies prior to and during the study
- Date of study completion and reason for early discontinuation, if applicable

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

Only designated individuals at the site will complete the CRFs. The CRFs must be completed at regular intervals following the clinical study visit schedule. It is expected that all data reported have corresponding entries in the source documents. The principal investigator is responsible for reviewing and certifying that the CRFs are accurate and complete. The only subject identifiers recorded on the CRFs will be subject number, and subject demographic information.

13.3 Data Review and Clarifications

A review of CRF data to the subject's source data will be completed by the site monitor to ensure completeness and accuracy. After the CRFs have been completed, additional data clarifications and/or additions may be needed as a result of the data cleaning process. Data clarifications are documented and are part of each subject's CRF.

13.4 Sponsor and Monitoring Responsibilities

The study sponsor will select principal investigators that are qualified by education, training, and experience to assume responsibility for the proper conduct of this clinical trial. For this study, the principal investigator and sub investigators must be health care professionals appropriately licensed to perform vitreoretinal and cataract surgery.

The study sponsor is financially funding this clinical trial and will compensate the investigator and/or the institution(s) at which the study is conducted in accordance with a signed clinical trial agreement.

The study sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals according to the study monitoring plan. The clinical investigation will be monitored to ensure that the rights and wellbeing of the subjects are protected, the reported data are accurate, complete, and verifiable from the source documents, and the study is conducted in compliance with the current approved protocol (and amendments[s], if applicable), with current GCP, and with applicable regulatory requirements.

The site may not screen subjects or perform the informed consent process on any subject until it receives a notification from an appropriate study sponsor representative that the site may commence conducting study activities. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written, and fax correspondence. Close-out visits will take place after the last visit of the last subject at the site.

Videos of surgery should be maintained with subject records for verification as source data and sent to sponsor for review as requested. Such data will be coded with a subject number only and will not contain subject personal information.

A coordinating investigator may be identified by the study sponsor to review and endorse the final study report. In cases where a coordinating investigator is engaged, the study sponsor will select the coordinating investigator based upon their experience, qualifications, active study participation, and their willingness and availability to take on this role.

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13.5 Regulatory Documentation and Records Retention

The investigator is required to maintain up-to-date, complete regulatory documentation as indicated by the study sponsor and the investigator's files will be reviewed as part of the ongoing study monitoring. Financial information is to be kept separately.

Additionally, the investigator must keep study records and source documents consistent with the terms of the clinical study agreement with the study sponsor. If the investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, then the study sponsor must be notified, and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations.

13.6 Quality Assurance and Quality Control

The study sponsor will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring and auditing by the study sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements made by the study sponsor with the investigator/institution and any other parties involved in the clinical study will be provided in writing as part of the protocol or as a separate agreement.

14 ETHICS

Investigations are conducted in compliance with GCP; international and national regulations, laws and guidelines; ISO 14155:2020; the conditions of approval imposed by reviewing IRBs/IECs or regulatory authorities; and in accordance with the ethical medical research principles outlined in the Declaration of Helsinki.

- The SOPs of the study sponsor and contract research organizations participating in the conduct of the clinical study and all other applicable regulations shall apply.
- Notifications and timelines for reporting protocol deviations should be based upon applicable ethics committee requirements.

The investigator must ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience. The investigator and all clinical study staff must conduct the clinical study in compliance with the protocol. The investigator is not allowed to deviate from the protocol except to protect the rights, safety, and wellbeing of human subjects under emergency circumstances. Emergency deviations may proceed without prior approval of the sponsor and the IRB/IEC but shall be documented and reported to the sponsor and the IRB/EC as soon as possible. Deviations from this protocol, regulatory requirements, and/or GCP must be recorded and reported to the sponsor prior to database lock. If needed, corrective and preventive action should be identified, implemented, and documented within the study records. Failure to implement identified corrective and preventative actions may result in site closure by the sponsor. Use of waivers to deviate from the clinical protocol is prohibited.

Before clinical study initiation, this protocol, the informed consent form, if applicable, any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an IRB/IEC. The investigator must provide documentation of the IRB/IEC approval to the study sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, assent form (if any), all applicable recruiting materials, written information for subject, and subject compensation programs. The IRB/IEC must be provided with a copy of the investigator's brochure, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. Any additional requirements imposed by the EC or regulatory authority shall be followed. At the end of the study, the investigator must notify the IRB/IEC about the study's completion. The IRB/IEC also must be notified if the study is terminated prematurely. Finally, the investigator must report to the IRB/IEC on the progress of the study at intervals stipulated by the IRB/IEC.

Voluntary informed consent must be obtained in writing from every subject. The obtaining of consent shall be documented before any procedure specific to the clinical investigation is applied to the subject.

The investigator must have a defined process for obtaining the required consent. Specifically, the investigator, or their delegate, must explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the investigator, and if required by local regulation, other qualified personnel. The investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and provide subjects with information

regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the IP and the study, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and must be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also must be told that their records may be accessed by appropriate authorities and sponsor-designated personnel. The investigator must keep the original, signed copy of the consent (file in subject's medical records) and must provide a duplicate copy to each subject according to local regulations.

The investigator must have a defined process in case a subject would like to withdraw their consent (s). The investigator is the designated contact point for any such withdrawals.

The investigator must have a defined process in case a subject would like to exercise any of their rights under applicable data protection laws. The investigator is the designated contact point for any such requests.

The study sponsor assures that the key designs of this protocol will be registered on public databases where required by current regulations, and, as applicable, results will be posted.

15 REFERENCES

15.1 Regulations and Standards

The following references may be applicable in whole or in part for this clinical trial.

- EN ISO 14155:2020 - Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice
- EU MDR: Regulation (EU) 2017/745 of the European Parliament and of the Council
- 21 CFR Part 11 - Electronic Records; Electronic Signatures
- 21 CFR Part 50 - Protection of Human Subjects
- 21 CFR Part 56 - Institutional Review Boards
- 21 CFR Part 812 - Investigational Device Exemptions
- 21 CFR Part 54 - Financial Disclosure by Clinical Investigators
- The California Bill of Rights, if applicable

15.2 Scientific and Other References

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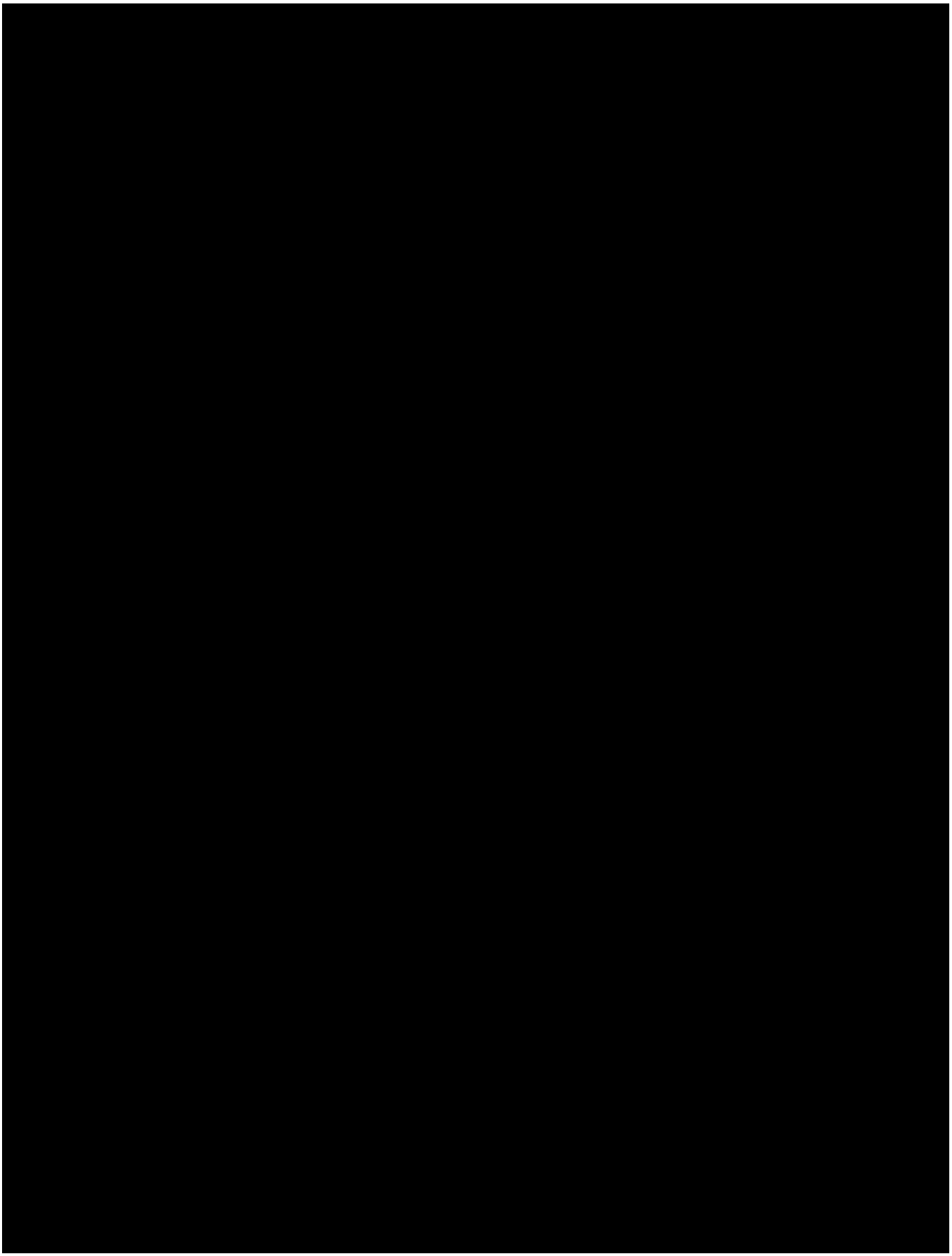

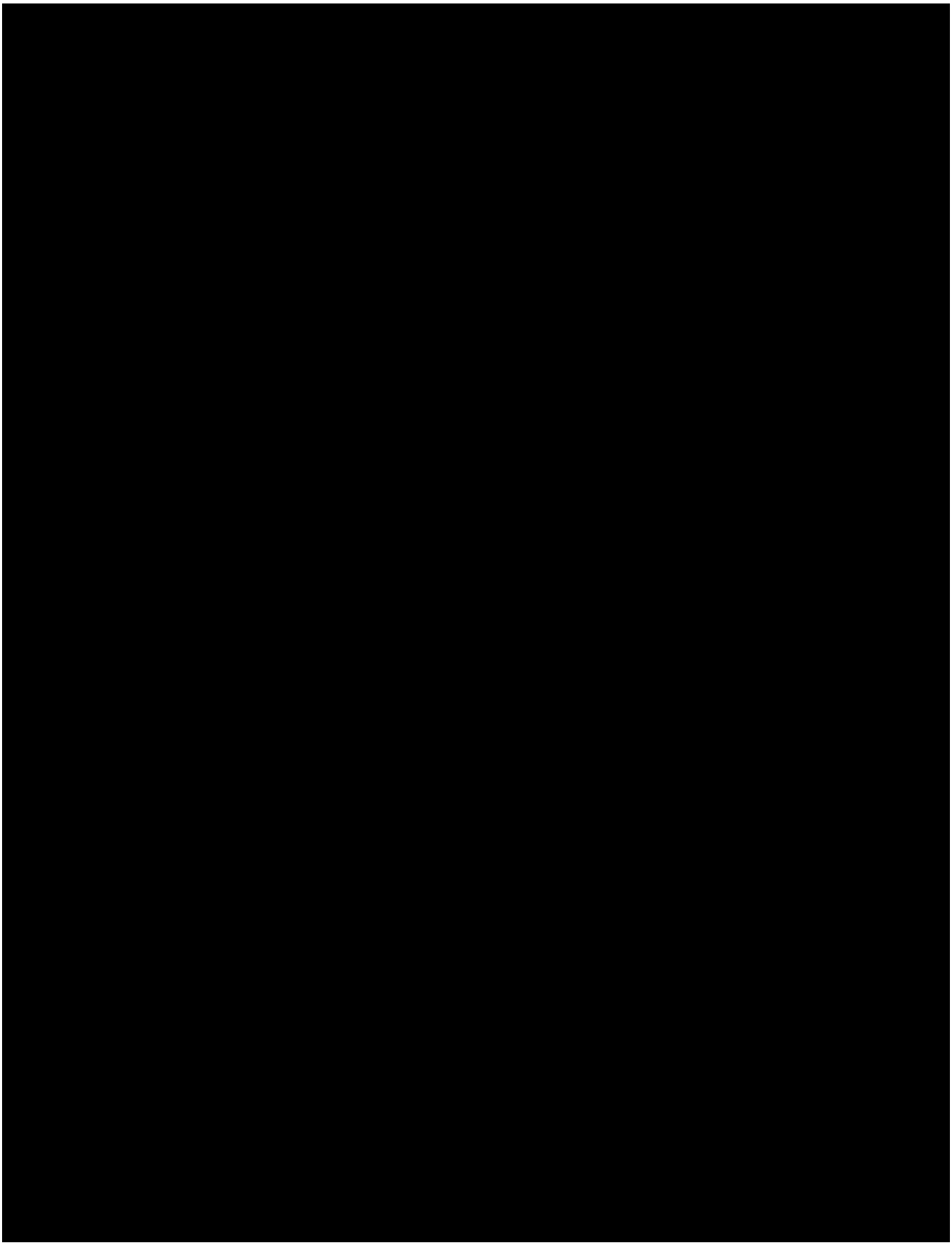

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