**Clinical Trial Protocol**

# Physiologic Phacofluidics: Ghost Protocol


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**Physiologic Phacofluidics: Ghost Protocol**

**Protocol V4.0**

**Date: 9/30/2023**

**Purpose:** To investigate the early post-operative clinical benefits when performing phacoemulsification at physiological intraocular pressure (IOP) using Centurion® Vision System with Active Sentry® handpiece

**Background:** Phacoemulsification and intracapsular lens implantation is the most common performed eye surgery to correct vision loss and restore vision for patients with cataract. During phacoemulsification, the ocular environment changes because of the heat generated by dissipated ultrasound energy, high perfusion, fluctuation in intraocular pressure (IOP), and the inflammatory response resulting from surgical manipulation.

Historically, the advances of phacoemulsification cataract surgery technologies have been geared towards increased efficiency of cataract removal, decreasing intra-operative complications, and faster post-operative visual recovery. A long-standing dogma of phacofluidics has been that high non-physiologic IOP settings (>65 mm Hg) are required for highly efficient cataract extraction However, studies are showing that operating at lower IOPs levels are as safe and efficacious[1]; and "physiological phaco" between 20-30mmHg may yield additional intra-operative and post-operative benefits:

- The lack of significant and rapid pressurization changes will result in significantly less early corneal edema in after cataract surgery[2]
- The normotensive intra-operative environment is gentler on the corneal endothelium resulting in clearer and healthier corneas in the short and long term; Some suggest that an increase in central corneal thickness (CCT) on the first postoperative day correlates with surgical trauma to the endothelium and that it is proportional to cell loss at 3 months[3]
- The Active Sentry (AS) Handpiece can maintain anterior chamber stability at low IOP settings, thus providing added safety and a gentler intra-operative environment[1, 4]
- Elicit a lower post-operative inflammatory response[2]

Several studies have looked at inflammatory indicators in FLACS (femtosecond laser-assisted cataract surgery) [8,9].

There has been minimal research on the clinical benefits in early post-op (initial hours after surgery) care and no studies evaluating inflammatory response in early post-operative stages with cataract surgery performed at near physiological IOP.

As cataract surgeons ever strive towards matching the speed of recovery and accuracy of visual outcomes of our corneal refractive counterparts, near physiologic phacoemulsification with the safety of the Centurion Active Sentry handpiece combined with low IOP phacoemulsification settings will likely be a key technological step forward towards that goal.

## Methods:

### Study population

### Inclusion Criteria

- Patients without prior ocular surgery both eyes
- Adult patients with visually significant cataract with WHO-World Health Organization NUC grade 2-3
- First eye only undergoing uncomplicated cataract surgery
- Unremarkable systemic history; controlled diabetes with HbA1c <7%
- Unremarkable ocular health
- Anterior chamber depth ACD >2.04mm[10]
- Age range 55-95

### Exclusion Criteria:

- Prior ocular surgery including corneal refractive surgery, cataract surgery in fellow eye
- Thin corneas (<490 microns)
- Complicated (use of pupil expansion devices) or prolonged cataract surgeries (>15 mins) with post-operative complications (IOP spike >30mmHg), severe punctate keratitis

Approximately 66 patients will be identified and included in the study. Patients at the day of surgery sign up will be randomized to high (65mmHg) vs low IOP (20mmHg) using a random online number generator; Even will be high IOP; Odd will be low IOP. Patients will undergo standard cataract surgery with equivalent vacuum and aspiration rates in both groups for the duration of the entire cataract surgery; IOP settings will be set at high vs low IOP but may be adjusted if necessary for the safety of the patient.

In all procedures, the intraocular lens (IOL) implanted and the ophthalmic viscosurgical device (OVD) materials used will be standardized to the same materials and are part of routine surgery. Cumulative dissipated energy (CDE) and surgical duration will be collected for all patients. An intraoperative aqueous sample 100-150µL will be collected at the end of the case 2 minutes after OVD removal and immediately transferred on dry ice to a laboratory, stored at -80°C until analysis as established in prior protocol.[6] The extraction of aqueous sample will not require additional incisions.

All subjects will be prescribed the standard post-operative cataract surgery medications (not specific to study). Post-operative visits by the masked sub-investigator will perform the following procedures at 4hrs (early post-op), POD#1 (20-24hrs), POW#1:

| **Post-op Procedures** | **Baseline** | **Visit1 (4hrs)** | **Visit2 (20-24hrs)** | **Visit3 (1 week)** |
|---|---|---|---|---|
| Pachymetry | X | X | X | X |
| Visual acuity | BCVA | UCVA/PHVA | UCVA/PHVA | UCVA/PHVA |
| Slit Lamp- Cell /Flare | X | X | X | X |

Pachymetry: a painless, simple test where a probe is gently placed on the front of the eye to measure the thickness of the cornea.

Best-corrected visual acuity (BCVA): this test is used to determine the smallest letters that can be read on a standardized chart. Un-corrected visual acuity (UCVA): the smallest letter that can be read unaided. Pinhole visual acuity (PHVA): the smallest letter that can be read without the interference of optical problems.
Slit lamp exam: a microscope is used to provide a magnified view of different parts of the eye and to determine inflammation (cell/flare) that is common with any ophthalmic surgery.

Visual acuity and slit lamp examinations are part of routine post-operative care. Pachymetry measurements are for research purposes to determine if there's less corneal swelling after cataract surgery in the lower IOP group.

The primary end point is: difference in CCT post-op at 4 hours between High vs Low IOP groups. Secondary endpoints include: CCT at POD#1 and POW#1, Cell/Flare at POHr4 and POD1, and inflammatory markers: levels of prostaglandin IL-6, IL-8, IL-Iβ, TNF-α, PGE2, MCP-1. Aqueous samples will be sent with de-identified patient information and aqueous analysis will be performed by the University of California, Irvine Molecular Biology and Biochemistry Labs. The laboratory will be masked to which treatment the subject received and will only provide the aqueous analysis report for the study.
Any adverse events (AE) will be recorded in subject's medical charts as well as an adverse event log. AEs are classified as serious or non-serious; expected or unexpected; and study-related, possibly study-related, or not study-related. Serious AEs will be reported immediately to the regulatory authorities as per standard of care. The potential risks involved are that of standard cataract surgery with potential complications and side effects associated with any surgical procedure. These include but are not limited to: infection, macular edema, increased IOP, general risk of anesthesia and surgery, bleeding in the eye, and decreased vision. Some potential benefits include: improved visual acuity, decreased glare symptoms, lowered IOP, and faster visual recovery.

**Analysis:**

Primary endpoint: Difference in mean CCT change at 4 hrs post-surgery between high vs low IOP will be assessed using t-test with a P-value <0.05. Descriptive statistics will be used for the other secondary endpoints

**Sample Size Justification:**

In Vasavada et al[2]., the expected mean CCT change between the high vs low groups is hypothesized to be 32um, with a standard deviation of 40um. With a Type I/II error rate of alpha=0.05 and power=0.85, a sample size of 56 eyes are needed; additional 10 eyes to account for ~15 attrition; N=66

**Data Collection and Management:**

Data is recorded in a manner that reduces the risk of a breach of confidentiality. Password protected Microsoft Excel files will be utilized for this study and only accessible by authorized study personnel.

**Ethical and Regulatory Considerations:**
The study is conducted in accordance with the following:

Protocol and study-related plans and documents
• Local regulations, as applicable
• Good Clinical Practices, as outlined in the ICH Harmonized Tripartite Guideline for GCP (ICH
E6(R2))Ethical and Regulatory Considerations:
The study is conducted in accordance with the following:
• Protocol and study-related plans and documents
• Local regulations, as applicable
• Good Clinical Practices, as outlined in the ICH Harmonized Tripartite Guideline for CP (ICH
E6(R2))
• The ethical principles established by the Declaration of Helsinki
• Regional participant data protection laws and regulations
• Local IRB requirements

**Institutional Review Board (IRB):**
The study site will maintain an accurate and complete record of all reports, documents and other submissions made to the Institutional Review Board (IRB) concerning this protocol.
The investigator must supply ongoing study progress reports to the IRB, per local requirements, protocol deviations and amendments. In addition, the investigator must notify the IRB at the closure of the study.

**Informed Consent:**
It is the responsibility of the investigator and clinical coordinator to inform each subject of the purpose of this study, including possible risks and benefits and document the informed consent process in the subject's chart. Prior to entry into the study or initiation of any study-related testing, the subject must read, sign and date the informed consent form. If the subject's vision is impaired to the point where they cannot read the informed consent document, the document will be read to the subject. The person executing the consent must also sign and date the consent form. One original informed consent form is to be retained by the study site and a copy is to be given to the subject.

**Protocol Amendments:**
This protocol must be followed as written. Any change or addition to this protocol that impacts subject safety, or the validity of the study requires a written protocol

amendment that must be approved in writing by the IRB and any required regulatory authorities before implementation.

**Record Keeping and Retention:**
Data generated for the study should be stored in a limited-access file area and be accessible only to study personnel of the site. All reports and communications relating to study participants will identify participants only by subject identification number. Complete subject identification will be kept by the investigator. This information will be treated with strict adherence to professional standards of confidentiality.

The Investigator will retain a copy in the study file:
• A copy of the IRB approved informed consent form
• All original informed consent forms with required signatures
• All participant source documents, etc.
• All IRB correspondence (i.e., informed consent [including any approved revisions], protocol,
AE, advertisements, newsletters).

**Confidentiality:**
All clinical study findings and documents are regarded as confidential. Study documents (protocols and other material) must be stored appropriately to ensure their confidentiality.
The anonymity of participants must be maintained per applicable local and national laws. Subjects are specified on all documents by subject number but not by name. Documents that identify the subject, e.g., the signed ICF, must be maintained in confidence by the investigator.

**Publication:**
Data and information generated in this study are the exclusive property of the investigator and are confidential. At the end of the study, a clinical study report will be written. Publications of the results must be based on appropriate analyses and review of the complete data. Authorship may be determined based on enrollment of eligible subjects or contribution to the design, conduct, or interpretation of the study.

Investigators agree to have their names listed as an investigator in any publication reporting the results from this study, whether or not they are an author on the publication. The publication or presentation of any study results shall comply with all applicable privacy laws.

**IRB Considerations:** Pending

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