PROTOCOL MICOR-304-102
VERSION 4.0
JUNE 29, 2023

A PROSPECTIVE MULTICENTER STUDY TO ASSESS THE CLINICAL OUTCOMES OF CURRENT PHACOEMULSIFICATION APPROACH TO CATARACT EXTRACTION VERSUS THE MICOR SYSTEM DEVICE USING LOW ENERGY LENS EXTRACTION IN PATIENTS UNDERGOING CATARACT SURGERY

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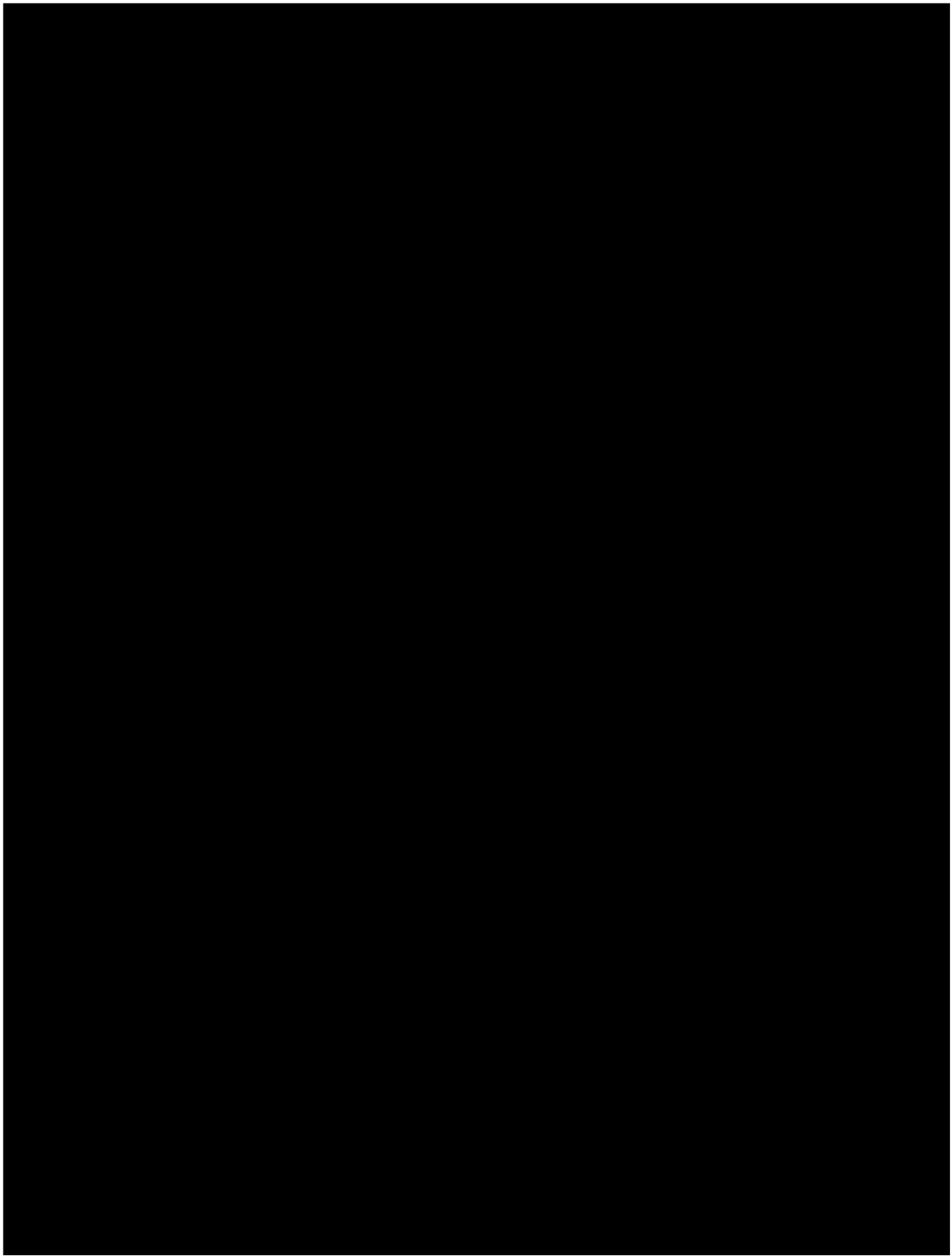

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VERSION 1.0

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2 INTRODUCTION AND RATIONALE

Background

Global estimates suggest that 94 million people are visually impaired due to cataract and, of these, 20 million are blind.[1] Because the incidence of cataracts increases with age, an increase in the elderly population will lead to a significant increase in cataract prevalence. Approximately 25% of people aged 65-69 years have cataracts, a proportion increasing to over 68% of those aged 80+ years.[2]

In 2014, nearly 23 million cataract surgeries were performed worldwide; of these, over 3.6 million procedures were performed each in the US and EU.[3] Cataract extraction with intraocular lens (IOL) implantation is the most commonly performed surgical procedure in the world. The safety and effectiveness outcomes of modern-day cataract surgery are well described in the literature.[4] Technological advances have transformed cataract surgery so that now over 99% are performed on an outpatient basis with excellent surgical outcomes.[5]

As cataract surgery has become minimally invasive and more procedural in nature, it has been performed much earlier in the course of disease and patients' lives. It is common to perform cataract surgery in the patient's 5th decade rather than their 70's even at extremely low levels of visual impairment. This early intervention has placed additional emphasis on safety and reduced ocular trauma during cataract surgery.

Current phacoemulsification approach to cataract extraction involves high-frequency thermogenic ultrasonic needle to fragment the lens and remove it from the anterior segment of the eye. This can be associated with significant ocular morbidity particularly in advanced cataracts because the phacoemulsification needle produces significant amount of energy and generates heat which is detrimental to the cornea and the endothelium.

Mechanical approaches to lens fragmentation and aspiration such as the MICOR System fragmentation and lens removal device provide an alternative to phacoemulsification with no cavitation, no thermogenic energy in the eye which can eliminate the generation of heat inside the eye while at the same time maintaining the same minimally invasive surgical approach through a small clear-cornea 2.5 mm incision.

[redacted]

3 STUDY OBJECTIVE

The purpose of this research study is to evaluate the clinical outcomes of current phacoemulsification approaches to cataract extraction involving high-frequency thermogenic energy versus the use of the MICOR System device using low-energy segment removal with a micro-interventional irrigation/aspiration port to evacuate the lens in subjects undergoing routine cataract surgery.

4. STUDY DESIGN

This is prospective, multicenter, 2-arm study designed to provide longitudinal, observational, clinical outcome data for the use of traditional phacoemulsification for subjects undergoing cataract surgery versus the MICOR System device used to evacuate the lens prior to intraocular lens insertion and cataract surgery. Only FDA cleared phacoemulsification devices can be used per indications.

4.1 Study Population

Both eyes of the study subjects may be enrolled into the study; however, if only 1 eye is eligible for study participation, then the eligible eye of the subject may be enrolled. Up to 960 eyes will be enrolled into one of two study groups at a maximum of 10 study centers. The 2 arms of the study groups are as follows:

- Group 1 Phaco subject cohort: this group will begin enrolling subjects initially with up to 510 eyes total.
- Group 2 MICOR System subject cohort, use of miLOOP optional to enroll subsequent to the Phaco cohort with up to 450 eyes total.

A sub-study cohort will be performed at 2 of the clinical study sites (Sites 03, and 06). The sub-study will involve collection of central corneal thickness measurements at the preoperative and 1-day postoperative visits. Central corneal pachymetry measurements will be performed using the Oculus Pentacam AXL. The 200 eyes added to the Phaco cohort will be enrolled into the sub-study cohort.

Individuals will be assessed for study eligibility based on the criteria presented below:

Inclusion Criteria

1. Able to understand study requirements, willing to follow study instructions and willing to return for required study follow-up visits.
2. Willing and able to understand and complete the informed consent document.
3. Subjects with a cataract grade of 1 to 4+ and are scheduled to undergo cataract surgery.
4. Subjects ≥ 18 years of age.

Exclusion Criteria

1. Subjects, who in the opinion of the investigator, have “compromised” eye(s); no comorbidities and no patients undergoing concurrent corneal surgery with cataract extraction.
2. Concurrent participation or participation in any clinical trial up to 30 days prior to preoperative visit.
3. Subjects that are pregnant, lactating or planning to become pregnant during the course of the study.

Primary Endpoint

- UCVA on day 1

Safety: Rate of occurrence of intraoperative and postoperative adverse events (AE)

Schedule of Visits

Screening visit, intraoperative visit, post-operative Day 1 (+2)

5 STUDY PROCEDURES

5.1 Subject Entry

Participants who meet the eligibility criteria will be asked to enroll in the study. The investigator or designee will explain the study purpose, procedures and responsibilities to the potential participant and provide sufficient opportunity to ask questions, while allowing adequate time for consideration of the information provided. Upon participant confirmation of interest, written informed consent will be obtained and the subject will be enrolled in the study. One copy of the informed consent document (ICD) will be retained with the subject's medical records and one copy will be provided to the subject.

Both eyes or only 1 eye per subject may be enrolled into the study. Up to 310 eyes will be enrolled into the Group 1 Phaco cohort and an additional 250 eyes will be enrolled into the Group 2 and Group 3 MICOR System cohorts. Overall, up to 810 study eyes may be enrolled into the study.

5.2 Procedure for Phacoemulsification

All subjects will undergo routine cataract surgical intervention with IOL implantation. All subjects will receive the standard of care preoperative and peri-operative medications and assessments. The procedure can be performed under either topical or peri/retrobulbar anesthesia per investigator discretion. Clear cornea cataract surgery using phacoemulsification will be performed using the following steps:

1. Topical or subtenon anesthesia
2. Viscoelastic
3. Capsulorhexis
4. Hydro-dissection

5. Creation of a superior or temporal clear corneal incision of 2.4 – 3.5 mm
6. Creation of two side port incisions at 2-3 clock hours on either side of the main wound
7. A phacoemulsification ultrasonic probe is used to the trench, emulsify, and aspirate the cataractous lens from the main wound
8. IOL implantation
9. Standard Post-operative antibiotics

5.3 Surgical Procedure for the MICOR System

All subjects will undergo routine cataract surgical intervention with IOL implantation. All subjects will receive the standard of care preoperative and peri-operative medications and assessments. The procedure can be performed under either topical or peri/retrobulbar anesthesia per investigator discretion.

5.4 Study Visits

All subjects enrolled will return for defined study visits pre- and post-operatively. Data collected from each scheduled and unscheduled (or interim) exam will be recorded on a Case Report Form (CRF). Subjects who become ineligible for study participation after enrollment will be exited from the study and the reason for exit will be documented on the Subject Screening Log

and noted as a screen failure. Screen failure subjects will be replaced with eligible study participants.

5.4.1 Pre-Operative/Screening Visit

Th pre-operative/screening visit can occur 0 to 90 days prior to the surgical procedure. The following information will be captured for the study eye at this visit:

- Demographic data (gender, age, race / ethnicity)
- Identification of study eye(s), OU, OD or OS
- Cataract type and grade
- Manifest Refraction
- Uncorrected Distance Visual Acuity (UCDVA)
- Best-corrected visual acuity (BCVA) – Snellen
- UCVA (pinhole)

5.4.2 Intraoperative

The following information will be captured for the study eye during surgery:

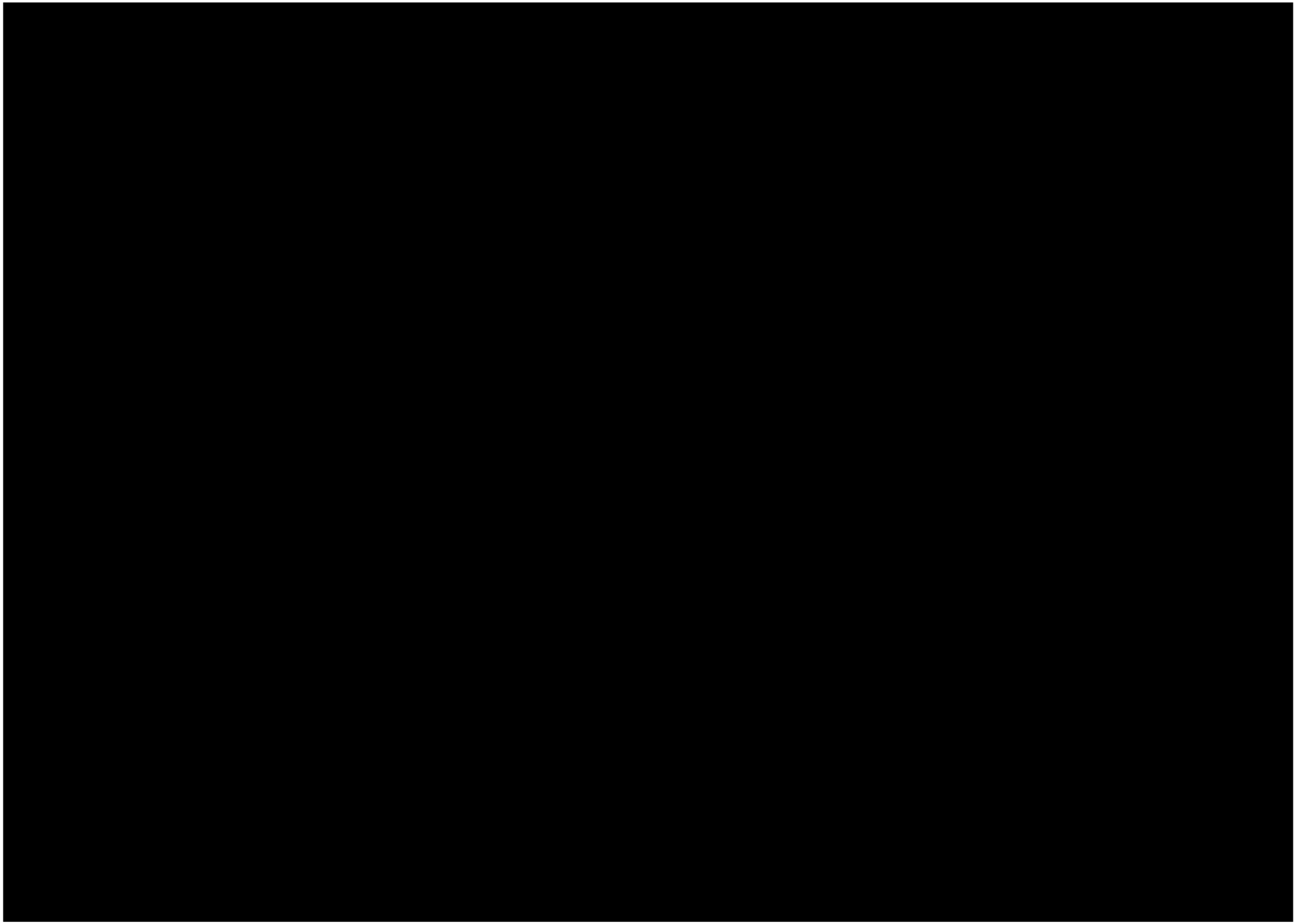
- Total lens removal time (i.e., MICOR tube in until MICOR I/A out, ready for IOL implantation or phaco needle in until phaco I/A out, ready for IOL implantation) –see **Figure 4**
- Failure to complete lens fragmentation with MICOR System
- Failure to complete lens extraction with MICOR System
- Failure to complete I/A with MICOR System
- Total volume of irrigation fluid used
- Other surgical procedures performed
- Cases not finished with MICOR I/A or Phaco
- Phaco energy used
- Device failure / malfunction
- Method / device used for cataract pre-segmentation (miLOOP, divide and conquer, horizontal chop, vertical chop, stop and chop, flip)
- Microscope type (heads up or standard scope)
- Cataract density grade
- Method used to patch subject eye (clear shield or patch and shield)
- MICOR System model used

- Any intraoperative AEs (capsule tear, corneal haze, other)

5.4.3 1 DAY Postoperative

This visit must occur at postoperative days 1-3. The following information will be captured for the study eye at this visit:

- Manifest Refraction
- Best-corrected visual acuity (BCVA) – Snellen
- Uncorrected distance visual acuity (UCDVA)
- UCVA (pinhole)
- AE assessment
- Macular OCT (optional)



The examinations associated with each study visit are outlined and summarized in **Table 1 below** (Schedule of Events and Procedures). A description of methodology for these examinations is provided in **Appendix 1** (Examination Procedures, Tests, Equipment and Techniques).

TABLE 1
SCHEDULE OF EVENTS AND PROCEDURES

PROCEDURE/EXAMINATION[1]	PREOPERATIVE & SCREENING (0 TO 90 DAYS PRIOR TO SX)	INTRA OPERATIVE (DAY 0)	1 DAY POSTOP (DAY 1-3)
Informed Consent / Demographics	X		
Surgical Procedure: Lens removal time, volume irrigation solution fluid used, other surgical procedures performed, device malfunction/failures, Pre-segmentation instrument / technique used, Failure to complete lens fragmentation with MICOR System, Failure to complete I/A with MICOR System, Phaco energy used, cataract grade, MICOR System model information		X	
Cataract type and grade	X	X	
BCVA Snellen	X		X
Manifest Refraction	X		X
UCVA	X		X
Pinhole VA at Day 1			X
AE Assessment		X	X

1 All procedures/examinations will be performed on the study eye(s) only

5.5 Unscheduled Visits

Unscheduled visits are those which are not required by the study protocol, but which occur due to a surgical procedure performed on the study eye, or a subject complaint regarding the study eye(s). No specific testing is required at unscheduled visits; rather, the Investigator and/or qualified investigational staff will perform the procedures necessary to evaluate the subject at these visits. Clinical data from these visits will be recorded on the relevant CRF.

5.6 Subject Identification

The subjects will be identified by a five-digit number comprised of a two-digit site number followed by a three-digit subject # (e.g., 01-001, 01-002, 01-003 etc.). The subject identification number will be assigned when informed consent is obtained.

5.7 Source Documents and Case Report Forms

Adequate original records will be maintained for the study. All original source documents will be retained at the site. The study sponsor, sponsor's representative, and appropriate regulatory authorities shall have access to the source documents as needed.

5.8 Device Deficiency

Record any and all problems experienced intraoperatively with the device. All device deficiencies should be reported to the Sponsor for investigation and documented on the Device Deficiency eCRF. Refer to the pertinent definitions provided in Table 2 below.

TABLE 2

DEVICE DEFICIENCY DEFINITIONS

Term	Definition
Device Deficiency	inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance Note 1 to entry: device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling Note 2 to entry: this definition includes device deficiencies related to investigational medical device or the comparator
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 investigational plan or investigator's brochure
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 1 to entry: use error includes the inability of the user to complete a task Note 2 to entry: use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment Note 3 to entry: users might be aware or unaware that a use error has occurred Note 4 to entry: an unexpected physiological response of the patient is not by itself considered a use error Note 5 to entry: a malfunction of a medical device that causes an unexpected result is not considered a use error

6 STATISTICAL METHODS

Analysis Plan

The primary endpoint will be analyzed with descriptive statistics. Point estimates and confidence intervals will be calculated for each outcome. Frequency tabulations of safety outcomes will be made at the 1-day follow-up evaluation.

Adverse Events

The number of subjects reporting at least 1 AE of a given type will be summarized. AEs not listed that occur during the study will be added to the summary of AEs. Summaries will also be provided for AEs considered to be related to the device. Each AE will be summarized by incidence and percentage.

7 ADVERSE EVENTS

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. If adverse events occur, the first concern will be the safety and welfare of the subject. Appropriate medical and/or surgical intervention will be taken. Any adverse event observed by the investigator or reported by the subject, regardless of severity and whether or not it is related to the investigational device, will be recorded on the Adverse Event Case Report Form. See Table 3 below for adverse event definitions.

AEs will be categorized by degree of harm to the subject (mild, moderate, or severe). Ocular conditions or diseases present at the time of study enrollment will be considered as “baseline.” Changes in a chronic condition or disease that are consistent with natural disease progression are not considered AEs.

Anticipated AEs that might reasonably be expected to occur include, but are not limited to, the following:

- Anterior chamber cell and flare requiring initiation of steroid treatment
- Capsular tear and rupture
- Vitreous loss
- Endophthalmitis
- Corneal edema
- Retinal tear / detachment

- Dialysis, flap tears or proliferative vitreoretinopathy
- Cystoid Macular Edema
- Hypopyon
- Hyphema
- Lens dislocation
- Dropped nucleus (or nuclear fragment) into vitreous cavity
- Pupillary block
- Acute corneal decompensation
- Raised IOP requiring treatment
- Severe inflammation
- Secondary Surgical Intervention

Table 3
Adverse Event Definitions

Term	Definition
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 and whether anticipated or unanticipated Note 1 to entry: this definition includes events related to the investigational medical device or the comparator Note 2 to entry: this definition includes events related to the procedures involved Note 3 to entry: for users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators
Serious Adverse Event (SAE)	adverse event that led to any of the following: • or injury, or permanent impairment to a body death, • serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function including chronic diseases, or o in-patient or prolonged hospitalization, or o medical or surgical intervention to prevent life-threatening illness structure or a body function,

Term	Definition
	• fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment Note 1 to entry: planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event Investigators must notify the Sponsor of any SAE as soon as possible, but no later than 10 working days from first learning of the event.
Unanticipated Serious Adverse Device Effect (USADE)	serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment Note 1 to entry: anticipated serious adverse device effect is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment Investigators must notify the Sponsor of any USADE as soon as possible, but no later than 10 working days from first learning of the event. The Sponsor will be responsible for informing Regulatory Authorities and all other Investigational Review Boards/Ethics Committees and investigators participating in the study of the USADE.
Severity	
Mild	Transient discomfort; no medical intervention/therapy required and does not interfere with daily activities
Moderate	Low level of discomfort or concern with mild-to-moderate limitation in daily activities; some assistance may be needed; minimal or no medical intervention/therapy required
Severe	Extreme discomfort and limitation in daily activities, significant assistance required; significant medical intervention/therapy required
Relatedness to Investigational Device	
Definitely Related	The adverse event has a strong temporal relationship to the study device and an alternative etiology is highly unlikely
Probably Related	The adverse event has a strong temporal relationship to the study device and an alternative etiology is less likely compared to the potential relationship to the study procedure

Term	Definition
Possibly Related	The adverse event has a possible temporal relationship to the study device, but an alternative etiology exists
Not Related	The adverse event is due to the underlying disease state or concomitant medication or therapy, and was not caused by the study device
Relatedness to Study Procedure	
Definitely Related	The adverse event has a strong temporal relationship to the study procedure and an alternative etiology is highly unlikely
Probably Related	The adverse event has a strong temporal relationship to the study procedure and an alternative etiology is less likely compared to the potential relationship to the study device
Possibly Related	The adverse event has a possible temporal relationship to the study procedure, but an alternative etiology exists
Not Related	The adverse event is due to the underlying disease state (e.g., glaucoma) or concomitant medication or therapy, and was not caused by the study procedure
Expedited Reporting of Adverse Events	
An AE should be classified as SERIOUS if it led to any of the following: • Caused or led to death. • Was life threatening (i.e., the AE placed the subject at immediate risk of death). • Required or prolonged inpatient hospitalization (i.e., the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay). • Was sight threatening. • Was disabling (i.e., the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions). • Resulted in a congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject due to participation in this study). Does not meet any of the above serious criteria but jeopardized the subject by requiring medical or surgical intervention to prevent one of the outcomes listed above.	

AEs will be followed until resolution or stabilization of the event.

Serious events or serious device related adverse events should be reported in accordance with the following requirements:

Event Type	Reporting Timeframe
USADE (Unanticipated Serious Adverse Device Event)	Within 24 hours of becoming aware of the event
SAE	ASAP but no later than 10 days of becoming aware of the event

Any ocular-related serious adverse event (SAE) should be reported to the study sponsor WITHIN ONE WORKING DAY of learning of the event. Non-ocular-related SAEs should be reported to the study sponsor within TWO WORKING DAYS of learning of the event. Email the Adverse Event CRF to gary@gsmservicesus.com and gneumann@regulatorypathways.com

Any serious device related adverse events must be reported to the following entities:

1. The study sponsor – Within ONE WORKING DAY of the investigator first learning of the event, email the AE CRF to gary@gsmservicesus.com; gneumann@regulatorypathways.com; and

2. The reviewing Institutional Review Board(IRB) Committee – As soon as possible, but no later than 7 working days after the investigator first learns of the event, report per the IRB instructions.

ALL adverse events (regardless of seriousness, severity, or relatedness) will be submitted to Andy Rybold at the following e-mail address: andy.rybold@zeiss.com for assessment of reportability to FDA under the reporting requirements for 21 CFR Part 803 Medical Device Reporting and compliance with complaint documentation under 21 CFR 820.198.

8 ETHICAL AND REGULATORY CONSIDERATIONS

This protocol was designed and will be conducted in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later amendments. Basic responsibilities of the study Investigators and overseeing Institutional Review Board(s) (IRB) are as noted below:

8.1 Investigator Responsibilities

The Investigator is responsible for maintaining clinical study records and reports as noted below for at least 2 years following the latter of: the date which the study is terminated or completed, or the date that the records are no longer required for purposes of supporting a marketing application. The Investigator will make these records available for audit and review by FDA as requested by the Agency.

Clinical Study Records:

- AEs
- Signed Investigator Agreements and Investigator *Curriculum Vitae* (CV)
- Financial disclosure information under 21 CFR Part 54
- Study Electronic Case Report Forms
- Study-related correspondence

Clinical Study Reporting:

- Results of evaluation of any serious device related adverse event to all Investigators, IRBs and FDA in accordance with reporting requirements under 21 CFR Part 803 Medical Device Reporting after receiving notice of the event
- Withdrawal of IRB approval to all Investigators, IRBs and FDA within 5 working days
- Progress reports to all IRBs annually or as required by the IRB
- Final report to all IRBs within 6 months of study termination or completion

8.2 Institutional Review Board

This protocol and the subject ICD must be reviewed and approved by an IRB operating in accordance with local procedures and 21 CFR Parts 50, 56, and 812 before enrollment of subjects.

The Investigator is responsible for maintaining IRB approval for the study protocol and ICD and for keeping the IRB informed of protocol amendments and AEs in accordance with IRB requirements.

The clinical trial information and the study outcome data will be posted on clinicaltrials.gov following the conclusion of the study and data analysis of the results.

9 REFERENCES

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2. Cataract surgeons outperform medical students in Eyesi virtual reality cataract surgery: evidence for construct validity. Selvander M, Asman P. Acta Ophthalmol. 2013 Aug;91(5):469-74. doi: 10.1111/j.1755-3768.2012.02440.x. Epub 2012 Jun 7.

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4. The phaco hemi-flip: a method of lens removal in nuclei of soft to moderate density. Tam DY, Ahmed II. Ophthalmic Surg Lasers Imaging. 2011 Mar-Apr;42(2):170-4. doi: 10.3928/15428877-20110316-04.

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[redacted]

APPENDIX 2: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, Republic of Korea October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.