



HRP-591 - Protocol for Human Subject Research

Protocol Title:

Prospective Comparison of Epinephrine and Phenylephrine/Ketorolac (Omidria®) Additives With Regards to Intraoperative Pupil Size

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Clinicaltrials.gov Registration #:

Not applicable

Important Instructions for Using This Protocol Template:

1. Add this completed protocol template to your study in CATS IRB (<http://irb.psu.edu>) on the “Basic Information” page, item 7.
2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
4. **For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (<http://irb.psu.edu>). For all other research, do not delete the instructional boxes from the final version of the protocol.**
5. When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (<http://irb.psu.edu>) for using track changes.

If you need help...**University Park and other campuses:**

[Office for Research Protections Human Research Protection Program](#)

The 330 Building, Suite 205
University Park, PA 16802-7014
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Fax: 814-863-8699
Email: irb-orp@psu.edu

College of Medicine and Hershey Medical Center:

[Human Subjects Protection Office](#)

90 Hope Drive, Mail Code A115, P.O. Box 855
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1. Objectives

1. Study Objectives

The purpose of this study is to compare the efficacy of phenylephrine 1.0%/ketorolac 0.3% (Omidria®) to epinephrine for intraoperative mydriasis (pupil dilation).

Our hypothesis is that phenylephrine/ketorolac additive is equal in efficacy to epinephrine with regards to its effects on pupil size during cataract surgery.

2. Primary Study Endpoints

The primary endpoint to be measured in the study is the mean area under the curve change from baseline in pupil diameter over time to the end of cataract surgery.

3. Secondary Study Endpoints

Secondary endpoints will be maximum intraoperative pupil constriction, subjects with pupil diameter less than 6.5 mm at any during surgery, subjects with pupil less than 6.0 mm during cortical clean-up, and subjects with greater than 2.5 mm of pupillary constriction at any time during surgery.

2. Background

2.1. Scientific Background and Gaps

Cataract remains a leading cause of correctable blindness worldwide. Over 3.5 million cataract surgeries in the United States and 20 million cataract surgeries worldwide are performed every year. Cataract surgery is performed by making a small incision, removing the cataractous lens, most often through the process of phacoemulsification, and replacement with an intraocular lens. Like all surgeries, adequate exposure and field of view is vital for a safe and effective surgery. In cataract surgery, the field of view is limited by the diameter of the pupil. Several different drugs, such as cyclopentolate, tropicamide, phenylephrine, and epinephrine are utilized to maintain dilation (mydriasis) of the pupil during surgery^{1,2}.

There are currently two prospective randomized controlled trials comparing phenylephrine/ketorolac to placebo in the published literature^{3,4}. Both of these studies demonstrated that phenylephrine/ketorolac is superior to placebo for the maintenance of mydriasis during cataract surgery. Epinephrine has been the standard of care for intraoperative mydriasis. Phenylephrine/ketorolac (Omidria) is a newly FDA-approved additive for the maintenance of intraoperative mydriasis, but there are currently no published studies comparing epinephrine to phenylephrine/ketorolac for maintenance of mydriasis during cataract surgery.

While both of these drugs have been shown to be superior to placebo for the maintenance of mydriasis, there is a significant cost difference between epinephrine, which has been used for many years, and phenylephrine/ketorolac, which gained FDA approval in 2014. One 4 mL vial of Omidria® is utilized for one cataract surgery, which costs \$465.

2.2. Previous Data

The two prospective randomized controlled trials comparing phenylephrine/ketorolac to placebo reported that phenylephrine/ketorolac was superior to placebo in maintaining intraoperative mydriasis, preventing miosis, and reducing postoperative pain. As previously mentioned, there is no currently reported data in the literature comparing phenylephrine/ketorolac to other commonly used mydriatic agents, such as epinephrine.

At our own center, we are currently performing a retrospective study comparing phenylephrine/ketorolac to epinephrine. There is no preliminary data at this time.

2.3. Study Rationale

Epinephrine is a current standard of care for intraoperative mydriasis during cataract surgery. Phenylephrine/ketorolac was approved by the FDA in 2014 and has been shown to be superior to placebo for maintenance of intraoperative mydriasis during cataract surgery. However, there has been no published literature on the efficacy of phenylephrine/ketorolac compared to epinephrine.

In addition, there is a significant cost difference between the current standard of care, epinephrine, (<\$20/dose) and phenylephrine/ketorolac (~\$400/dose).

3. Inclusion and Exclusion Criteria

3.1. Inclusion Criteria

- Patients who are older than 18 years of age
- Patients who are planned to undergo bilateral cataract surgery
- Patients with baseline IOP of 5 - 22 mm Hg
- Medicare insurance*

*As discussed in 2.3, there is a significant cost difference between our two study drugs. Therefore, Medicare insurance is part of our inclusion criteria, because there is a pass-through reimbursement in place to cover the cost of phenylephrine/ketorolac. Other insurances (for example, Aetna Better Health, Highmark Freedom, Gateway) have variable or poor coverage for phenylephrine/ketorolac, which would leave the medical center responsible for the cost. Patients can never be held responsible for the cost of the medication because it is included in “covered services” for cataract surgery billing.

3.2. Exclusion Criteria

- Patients who are planned to undergo only unilateral cataract surgery
- Patients who are planned to undergo cataract surgery and another surgical procedure in the same operation (eg. combined cataract and glaucoma surgery)
- Patients with concurrent clinically significant disease, connective tissue disease, abnormal blood pressure at screening, narrow-angle or unstable glaucoma or treatment with prostaglandins, uncontrolled chronic eye disease or active corneal pathology or scarring
- Patients with history of iritis or trauma with iris damage
- Patients with recent eye surgery (non-laser surgery within 3 months or laser surgery within 30 days prior to study surgery)

- Patients with clinically significant hypersensitivity to the study medications
- Patients who have used pilocarpine (a pupil constrictor) within 6 months prior to surgery

3.3. Early Withdrawal of Subjects

3.3.1. Criteria for removal from study

Subjects may withdrawal from the study if they no longer wish to participate in the study. Subjects may withdrawal from the study if they no longer plan to undergo bilateral cataract surgery. There are no anticipated safety reasons for which a subject would need to withdrawal from the study. There is no disease progression that would require a subject to withdrawal from the study.

3.3.2. Follow-up for withdrawn subjects

Subjects may withdrawal from the study at any point up to their second cataract surgery. Data will be collected for the number and the reason for withdrawal of subjects (eg. withdrawal of consent). A patient disposition flow diagram will be constructed. Subjects that withdrawal from investigational treatment will be treated as any other patient who is undergoing cataract surgery outside of the study.

4. Recruitment Methods

4.1. Identification of subjects

All patients meeting the inclusion criteria who are seen and evaluated in the ophthalmology clinics of the study team physicians and plan to undergo bilateral cataract surgery will be offered to participate in the study.

It should be noted that only eligible patients with Medicare insurance are to be offered the opportunity to participate in the study. This is because Medicare universally provides adequate reimbursement for Omidria, while other carriers (i.e. Gateway Heath or Amerihealth) do not.

4.2. Recruitment process

All patients will be offered the opportunity to participate in the study, will be provided information in person while being consented for cataract surgery, and will be given an informed consent form regarding the study.

4.3. Recruitment materials

An informed consent form will be used to recruit subjects.

4.4. Eligibility/screening of subjects

Patients will be asked eligibility questions before obtaining informed consent. Those who meet exclusion criteria will not be consented for the study.

5. Consent Process and Documentation

5.1. Consent Process

5.1.1. Obtaining Informed Consent

5.1.1.1. Timing and Location of Consent

Informed consent is a process. Consent will take place in the ophthalmology clinic when a patient would be regularly consented to undergo cataract surgery (within 60 days of surgery date). The average wait time for cataract surgery in our ophthalmology clinic is currently 30-60 days. As the patient presents for surgery, the consent will be reviewed once again and any additional questions will be addressed to confirm they still want to participate in the study.

5.1.1.2. Coercion or Undue Influence during Consent

All patients consenting for cataract surgery [that meet inclusion criteria](#) will be offered to participate in the study. They will not be persuaded to participate.

5.1.2. Waiver or alteration of the informed consent requirement

Not applicable

5.2. Consent Documentation

5.2.1. Written Documentation of Consent

Consent will be documented in writing through a consent document. This document will be uploaded and available for the study in CATS IRB.

5.2.2. Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Not applicable. Written consent will be obtained.

5.3. Consent – Other Considerations

5.3.1. Non-English Speaking Subjects

Not applicable

5.3.2. Cognitively Impaired Adults

5.3.2.1. Capability of Providing Consent

Not applicable

5.3.2.2. Adults Unable To Consent

Not applicable

5.3.2.3. Assent of Adults Unable to Consent

Not applicable

5.3.3. Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1. Parental Permission

Not applicable.

5.3.3.2. Assent of subjects who are not yet adults

Not applicable.

6. HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1. Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

Authorization will be obtained and documented as part of the consent process. *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained). *[Complete all parts of sections 6.2 and 6.3]*

6.2. Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1. Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1. Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2. Plan to destroy identifiers or a justification for retaining identifiers

Identifiers will not be recorded or retained.

6.2.2. Explanation for why the research could not practicably be conducted without access to and use of PHI

Access to PHI will be necessary to determine inclusion/exclusion criteria for a subject to enroll in the study.

6.2.3. Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Not applicable

6.3 Waiver or alteration of authorization statements of agreement

Not applicable

7. Study Design and Procedures

7.1. Study Design

This is a double-blinded prospective randomized controlled study of patients who are undergoing bilateral cataract surgery (separate unilateral operations performed within several weeks of each other). Patients will be selected to participate in the study based on inclusion/exclusion criteria. Each patient in the study will be randomly assigned to intracameral phenylephrine/ketorolac in one eye and intracameral epinephrine in the other eye for intraoperative mydriasis. A video will be recorded of the surgical eye for the entire duration of cataract surgery. A single reviewer will watch the video and record the pupil diameter for every minute during the duration of the surgery. The reviewer will be blinded to which eye received which mydriatic agent intraoperatively.

It should be noted that video recording of surgical procedures is a routine practice for many of the participating surgeons and is not limited to only those participating in the study. [Thus, it is not considered a 'study procedure,' but instead is routine practice.](#)

7.2. Study Procedures

7.2.1. EXAMPLE: Visit 1 or Day 1 or Pre-test, etc. (format accordingly)

Pre-operative visit: Inclusion/exclusion criteria will be assessed. Consent will be obtained from eligible subjects who wish to participate in the study. Demographic and baseline characteristics will be recorded.

7.2.2. EXAMPLE: Visit 2 or Day 2 or Post-test, etc. (format accordingly)

Day of surgery: Video recording of the surgical eye during the entire duration of surgery will be obtained.

Post-operative visits: Patients will be followed routinely post-operatively. No data will be collected from post-operative visits.

7.3. Duration of Participation

The individual subject will participate in the study for two cataract surgeries.

8. Subject Numbers and Statistical Plan

8.1. Number of Subjects

At least 106 subjects will need to be accrued. This is assuming that no subjects will drop out of the study once they are accrued.

8.2. Sample size determination

106 subjects assumes there will be a 0.3 mm difference between the two treatment arms, alpha = 0.05, power = 95%. A difference of 0.3 mm was assumed based on the results of two previous trials that had a difference of 0.6 mm comparing phenylephrine/ketorolac to placebo^{3,4}.

8.3. Statistical methods

The trapezoidal rule will be used to calculate the AUC of pupil diameter from surgical baseline to wound closure. The result will be divided by time of the last pupil diameter value to determine mean AUC. Baseline pupil diameter will then be subtracted from the mean AUC. A chi-square test will be used to compare continuous data between the two treatment arms.

9. Confidentiality, Privacy and Data Management

9.1. Confidentiality

9.1.1. Identifiers associated with data and/or specimens

See the Research Data Plan Review Form

9.1.1.1. Use of Codes, Master List

See the Research Data Plan Review Form

9.1.2. Storage of Data and/or Specimens

See the Research Data Plan Review Form

9.1.3. Access to Data and/or Specimens

See the Research Data Plan Review Form

9.1.4. Transferring Data and/or Specimens

See the Research Data Plan Review Form

9.2. Subject Privacy

See the Research Data Plan Review Form

10. Data and Safety Monitoring Plan

10.1. Periodic evaluation of data

Not applicable

10.2. Data that are reviewed

Not applicable

10.3. Method of collection of safety information

Not applicable

10.4. Frequency of data collection

Not applicable

10.5. Individuals reviewing the data

Not applicable

10.6. Frequency of review of cumulative data

Not applicable

10.7. Statistical tests

Not applicable

10.8. Suspension of research

Not applicable

11. Risks

Both of the study drugs are currently routinely used in cataract surgery. There are no risks in addition to the small risks associated with routine cataract surgery. There is a minimal risk of loss of confidentiality.

12. Potential Benefits to Subjects and Others

12.1. Potential Benefits to Subjects

There is no direct benefit to individual subjects, as both of the study drugs are routinely used during cataract surgery.

12.2. Potential Benefits to Others

Better mydriasis allows for a better view and operating field for the ophthalmologist, potentially leading to decreased difficulty of surgery and potentially better surgical outcomes. Benefits to society include potentially identifying an equally efficacious drug that is significantly cheaper. During a time when healthcare costs continue to rise, this is extremely relevant.

13. Sharing Results with Subjects

Not applicable

14. Subject Stipend (Compensation) and/or Travel Reimbursements

Not applicable

15. Economic Burden to Subjects

15.1. Costs

The subjects will not be responsible for any additional costs for participating in the research.

15.2. Compensation for research-related injury

There is no risk in addition to that of routine cataract surgery.

16. Resources Available

16.1. Facilities and locations

Patients will be recruited from the Penn State Hershey Eye Center Clinic (UPC 1, Suite 800). All cataract surgeries for the study will be performed at Hershey Outpatient Surgery Center (HOSC).

16.2. Feasibility of recruiting the required number of subjects

The study team has access to approximately 10-20 potential subjects per week. At a minimum, 10% of subjects (1-2 per week) would need to be recruited in a one year period to reach the required number of participants for the desired study power.

16.3. PI Time devoted to conducting the research

The PI has 20% academic time and will be contributing half of this to research activities, for a total percentage effort of 10%.

16.4. Availability of medical or psychological resources

Not applicable

16.5. Process for informing Study Team

Team members will meet with the PI every second and fourth Monday of each month during the course of the study to ensure proper training on study protocol and duties.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

Clinical Research Center (CRC) Advisory Committee – All campuses – Research involves the use of CRC services in any way.

Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute

Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: <http://www.pennstatehershey.org/web/irb/home/resources/investigator>

18.0 Multi-Site Research

18.1 Communication Plans

Not applicable

18.2 Data Submission and Security Plan

Not applicable

18.3 Subject Enrollment

Not applicable

18.4 Reporting of Adverse Events and New Information

Not applicable

18.5 Audit and Monitoring Plans

Not applicable

19.0 Adverse Event Reporting

19.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored

Not applicable

21.2 Location of storage

Not applicable

21.3 Duration of storage

Not applicable

21.4 Access to data and/or specimens

Not applicable

21.5 Procedures to release data or specimens

Not applicable

21.6 Process for returning results

Not applicable

22.0 References

¹Grob SR, Gonzalez-Gonzalez LA, Daly MK. Management of mydriasis and pain in cataract and intraocular lens surgery: review of current medications and future directions. *Clin Ophthalmol.* 2014; 8: 1281-1289.

²Lawuyi LE, Gurbaxani A. The clinical utility of new combination phenylephrine/ketorolac injection in cataract surgery. *Clin Ophthalmol.* 2015; 9: 1249-1254.

³Hovanesian JA, Sheppard JD, Trattler WB, et al. Intracameral phenylephrine and ketorolac during cataract surgery to maintain intraoperative mydriasis and reduce postoperative ocular pain: integrated results from 2 pivotal phase 3 studies. *J Cataract Refract Surg.* 2015; 41: 2060-2068.

⁴Lindstrom RL, Loden JC, Walters TR, et al. Intracameral phenylephrine and ketorolac injection (OMS302) for maintenance of intraoperative pupil diameter and reduction of postoperative pain in intraocular lens replacement with phacoemulsification. *Clin Ophthalmol.* 2014; 8: 1735-1744.