PROTOCOL FOR CLINICAL INVESTIGATION – NON-EXEMPT HUMAN
(Wilford Hall Ambulatory Surgical Center – WHASC)

PROTOCOL SUMMARY

1. Title:

Post-operative pain control after photorefractive keratectomy comparing acetaminophen/codeine vs acetaminophen/oxycodone
FWH20160007H

2.0. Principal Investigator (PI):

	WHASC PI:	**Co-PI:**
Name	**Charisma Evangelista**	
Rank/Corps or Civilian Rating	**Maj/MC**	
Date of IRB Approved CITI Training	**6 Sep 2017**	
Branch of Service	**USAF**	
AD Mil/DoD Civilian/Ctr/Non-DoD Civ	**AD Mil**	
Department & Base	**Dept of Ophthalmology/Lackland AFB**	
Phone & Pager #	**292-4700/ 594-0521**	
E-Mail Address & AKO/DKO E-Mail Address	**charisma.b.evagelista.mil@mail.mil**	
DoD Assurance # and Expiration Date	**N/A**	

3.0. Research Plan:

3.1. Purpose:
To determine any differences in perceived post-operative pain control using different forms of opioid pain medication. This will provide insight into the need to use medications with higher abuse potential.

3.2. Hypotheses, Research Questions or Objectives:
Is there a difference in the perceived post-operative pain levels of patients undergoing photorefractive keratectomy when using codeine versus oxycodone for pain control?

4. Brief Summary of the study:
Photorefractive keratectomy (PRK) is a refractive error correction procedure that helps eliminate or reduce the dependence on corrective lenses. An important aspect of PRK is post-operative pain management. Post-operative pain can be significant in the first three to five days and is typically controlled utilizing various modalities including narcotic pain medication. Simple observation suggests a difference in the post-operative pain levels of patients utilizing the more potent oxycodone- versus the less potent codeine-containing acetaminophen preparations. There have been no studies performed to explore any differences in perceived pain comparing these two medications when used following PRK. This study is designed to answer this question by means of a pain survey conducted in the first five days post-op. This may help better manage similar patients in the future.

5. Subjects:
Patients referred to the Joint Warfighter Refractive Surgery Center at WHASC. This population includes active duty members but excludes pregnant women, children, military basic trainees, prisoners, and detainees.

6. Inclusion/exclusion criteria:
Inclusion criteria:
Patients included for this study will be active duty members and DoD beneficiaries referred to the Joint Warfighter Refractive Surgery Center for corrective refractive surgery. This population generally includes healthy individuals of age groups 21 years of age and above. Inclusion criteria are:

- M/F ≥21 years of age (PRK is not done on anyone under the age of 21 at this surgery center)
- Have met all criteria for bilateral PRK

Exclusion criteria:

- Patients who do not meet the criteria for refractive surgery
- Patients receiving LASIK
- Patients known to have an allergy to either of the study pain medications

- Patients receiving refractive surgery on only one eye
- Pregnant women, children, military basic trainees, prisoners and detainees
- Subject has used narcotics in the last 6 months

7. Number of Subjects: TOTAL NUMBER OF SUBJECTS (nation-wide/study-wide): WHASC 200

8. Use of an Investigational New Drug: N/A

9. Use of an Investigational Device: N/A

10. Use of a Placebo: N/A

PROTOCOL FOR CLINICAL INVESTIGATION – NON-EXEMPT HUMAN
(Wilford Hall Ambulatory Surgical Center – WHASC)

1. Title:

Post-operative pain control after photorefractive keratectomy comparing acetaminophen/codeine vs acetaminophen/oxycodone
FWH2016007H

2.0. Principal Investigator (PI):

	WHASC PI:	**Co-PI:**
Name	**Charisma Evangelista**	
Rank/Corps or Civilian Rating	**Maj/MC**	
Date of IRB Approved CITI Training	**6 Sep 2017**	
Branch of Service	**USAF**	
AD Mil/DoD Civilian/Ctr/Non-DoD Civ	**AD Mil**	
Department & Base	**Dept of Ophthalmology/JBSA-Lackland**	
Phone & Pager #	**292-4700/ 594-0521**	
E-Mail Address & AKO/DKO E-Mail Address	**Charisma.b.evangelista.mil@mail.mil**	
DoD Assurance # and Expiration Date	**N/A**	

2.1. Associate Investigators (AI):
Provide the current list of all "engaged" AIs for the study based on 45 CFR 46.102, e.g., for purposes of research the AI: (1) obtains data through intervention or interaction with a research subject(s); and/or (2) obtains identifiable private information and/or protected health information about the research subject(s); and/or (3) obtains the informed consent of human subjects for research. **All "engaged" investigators must complete IRB approved CITI training.**

Name	**AD/DoD Civ/Ctr/ Non-DoD Civ**	**Rank/Corps or Civilian Rating/Title**	**Date of CITI Training**	**Phone & Pager #**
Mathew Caldwell	**AD**	**Lt Col**	**2~~0~~5 Oct 2018~~5~~**	**292-2010**
Gary Legault	**AD**	**MAJ (USA)**	**14 Feb 2017**	**292-2010**
Darrel Carlton	**AD**	**COL (USA)**	**25 Jul 2017**	**292-4700**
Vasudha Panday	**Ctr**	**Ophthalmologist**	**0~~4~~5 Oct 2018~~5~~**	**292-2010**
Douglas Apsey	**Ctr**	**Optometrist**	**1~~2~~7 Sep 2018~~5~~**	**292-2554**
P. David Kohler	**Ctr**	**Optometrist**	**2~~3~~2 Jan 2018~~5~~**	**292-2584**
Robert E. Smith	**Ctr**	**Ophthalmologist**	**01 Aug 2017**	**292-2010**
Donovan Reed	**AD**	**Capt/MC/Ophthal. Resident**	**07 Jul 18**	**292-6995**

2.2. Research Assistants (RA) & Coordinators (RC):
Provide the current list of all "engaged" RAs & RCs for the study based on 45 CFR 46.102, e.g., for purposes of research the RA or RC: (1) obtains data through intervention or interaction with a research subject(s); and/or (2) obtains identifiable private information and/or protected health information about the research subject(s); and/or (3) obtains the informed consent of human subjects for research. **All "engaged" RAs and RCs must complete IRB approved CITI training.**

Name	**AD/DoD Civ/Ctr/ Non-DoD Civ**	**Rank/Corps or Civilian Rating/Title**	**Date of CITI Training**	**Phone & Pager #**
Kathleen Dinan	**Ctr**	**Ophthal. Tech/RC**	**24 Apr 2018**	**292-2565**
Catherine Hale	**Ctr**	**Ophthal. Tech/RA**	**01 Mar 2017**	**292-2483**
Linda Saavedra	**Ctr**	**Ophthal. Tech/RA**	**05 Oct 2017**	**292-2483**
Rita Garza	**Ctr**	**Ophthal. Tech/RA**	**02 Mar 2017**	**292-2483**
Christie Kaden	**Ctr**	**Ophthal, Tech/RA**	**1 Mar 2017**	**292-2483**

2.3. The research relevance of this protocol focuses on:
[ ] Diagnosis [x] Treatment [ ] Medical Utilization/Managed Care [ ] Prevention [ ] Medical Readiness [ ] Other
2.4. Location(s): Joint Warfighter Refractive Surgery Center at WHASC

3. Research Plan:

3.1. Purpose:

To determine any differences in perceived post-operative pain control using different forms of opioid pain medication. This will provide insight into the need to use medications with higher abuse potential.

3.2. Hypotheses, Research Questions or Objectives:
Is there a difference in the perceived post-operative pain levels of patients undergoing photorefractive keratectomy (PRK) when using codeine versus oxycodone for pain control?

3.3. Significance:
PRK is a safe and effective method of improving the vision of many patients but is attended by significant post-operative pain. Comparing pain management using narcotics with different potencies helps the clinician decide whether a stronger/more potentially addictive substance like oxycodone is necessary for adequate pain control.

3.4. Military Relevance:
Laser refractive surgery in the United States Air Force has developed into a robust program since its inception in 2001.[1] Of the different surgical corrective options, PRK has been the most commonly performed refractive surgery in the United States Armed Forces.[1,2,3] It is utilized in the military to help reduce dependence on corrective eye wear and thus increase readiness and mission operations. Improving the overall experience of photorefractive keratectomy including pain control would help maintain or increase its perception as a valuable treatment option for refractive error.

3.5. Background and Review of Literature:
PRK is a surgical procedure that utilizes a laser to reshape the surface (cornea) of the eye, allowing for greater or even complete independence from corrective eye wear. It may have less risk of corneal destabilization and dry eye when compared with the more commonly performed procedure laser in situ keratomileusis (LASIK).[4,5] However, pain and discomfort is an important limitation of PRK, particularly post-operatively as pain peaks approximately 24 hours and then gradually subsides as the corneal epithelium heals.[6] Various strategies to minimize post-operative pain are an ongoing effort.[7] At our institution a recent change in post-operative analgesic prescribing practices (switching from oxycodone to codeine as the primary narcotic pain controller) has led to the anecdotal perception that oxycodone may control pain better than codeine. There are no studies in the literature that address subjective pain experienced post-operatively comparing these two pain control modalities when used following PRK. If this survey finds that there is a difference in perceived post-operative pain between patients using oxycodone versus codeine, then it may help clarify the post-PRK pain medication regimen.

3.5.1. Bibliography:

1. Panday VA, Reilly CD. Refractive surgery in the United States Air Force. Curr Opin Ophthalmol, 2009; Jul(4):242-246
2. Hammond MD, Madigan WP, Bower KS. Refractive surgery in the United States Army, 2000-2003. Ophthalmology, 2005; Feb:112(2):184-90.
3. Stanley PF, Tanzer DJ, Schallhorn SC. Laser refractive surgery in the United States Navy. Curr Opin Ophthalmol, 2009; Jul 19(4):321-324.
4. Spadea L, Cantera E, Cortes M, Conocchia NE, Stewart CW. Corneal ectasia after myopic laser in situ keratomileusis: a long-term study. Clin Ophthalmol. 2012;6:1801-13.
5. Lee HK, Lee KS, Kim HC, Lee SH, Kim EK. Nerve growth factor concentration and implications in photorefractive keratectomy vs laser in situ keratomileusis. Am J Ophthalmol. 2005 Jun;139(6):965-71.
6. McCarty CA, Garrett SK, Aldred GF, et al. Assessment of subjective pain following photorefractive keratectomy. Melbourne Excimer Laser Group. J Refrac Surg, 1996; Mar-April 12(3):365-369.
7. Woreta FA, Gupta A, Hoschstetler B, Bower KS. Management of post-photorefractive keratectomy pain. Surv Ophthalmol, 2013; Nov-Dec 58(6): 529-535.

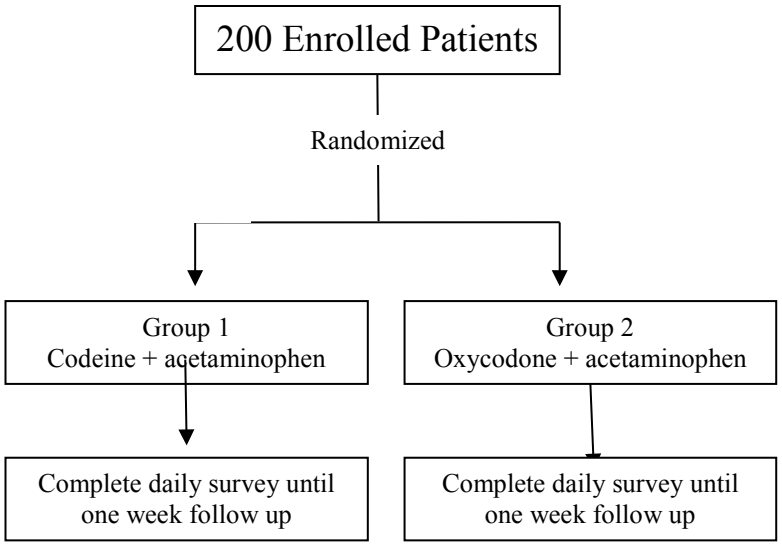
3.6. Research Design and Methods:
This will be a prospective pain assessment study utilizing a simple three question survey given to patients undergoing bilateral PRK. Following recruitment and enrollment (see section 4.1 and 4.2 for recruitment and consent process), patients will be randomized to be prescribed either 1) Group 1: codeine 30mg/acetaminophen 300mg (standard of care dosage) or 2) Group 2: oxycodone 5mg/acetaminophen 325mg (standard of care dosage) post-operatively. All post-operative patients will receive standard bandage contact lenses and as needed tetracaine as per standard of care. Patients will be removed from the study if they take other non-study pain medications. They will be asked to record their pain levels four times daily as well as the number of as needed narcotic pain medication taken and the number of tetracaine drops used (to isolate a potential confounding pain control modality). Randomization will be performed with the aid of www.randomizer.org which will generate a randomized assignment to either group 1 or group 2.

All PRK procedures will be performed per standard of care. The procedure will be performed by one of the 4 approved surgeons. All surgeons will use the same technique using either the VISX or the Allegretto laser machines. This technique will include use of a brush for mechanical removal of corneal epithelial cells. The surgeons will take note at this time of the relative adherence of the epithelium to the underlying tissue and grade the adherence on a scale of 0-4 (0=least adherent and 4=most adherent). In the data analysis, differences between surgeons and between operating platform (VISX vs Allegretto) will be compared to account for any possible bias in operating parameters.

The survey will be worded as follows:

1. "Rate your eye pain or level of discomfort at 0800, 1200, 1600 and 2000. Please **write** the number closest to your response in the table below under the appropriate day and time.
2. "How many tablets of study-related pain medication did you take today in the AM/PM?"
3. "How many times did you use topical tetracaine today in the AM/PM?"
4. "Did you take any other non-study related pain medications?"

Patients will be followed-up post-operatively as per standard of care. This includes follow-up visits at 1 day, 1 week, 1 month, 3 months, 6 months and 12 months. Starting on post-operative day 1, the patients will be asked to record their pain levels using the pain survey at four hour intervals (0800, 1200, 1600, 2000). At the 1 week post-operative visit, the pain surveys will be collected from the patients. Visual acuity data will be extracted from all but the 12 month follow-up appointment and used as a secondary outcome to correlate any possible differences in pain scores to functional outcomes in terms of visual acuity.



3.6.1. Interventions, Observations, or Data Sought:
Primary Outcome: Subjective median daily post-operative average pain score following PRK in each eye
Secondary Outcomes: Post-operative visual acuities (standard of care), which surgeon performed the surgery, adherence of epithelium to underlying tissue, which laser platform was used, side effects from the study medications requiring a change or cessation of the pain control medication.

3.6.2. Data Collection and Processing:
The pain surveys will be collected from each subject at the 1 week post-operative visit. The secondary outcomes listed in 3.6.1. are standard of care information and will be recorded from the subjects clinical records.

3.6.3. Setting: Joint Warfighter Refractive Surgery Center at WHASC

3.6.4. Date(s): 1 December 2015-31 May 2017

3.6.5. Source of Research Material:

Source of Research Material per Participant (Procedures)	# Routine Care	# Research Driven	# Total Procedures
Pain Survey (1 day, 1 week)	0	8	8
JWRSC Clinical Record—Visual Acuity (1 day, 1 week), surgeon, laser platform	5	0	5

3.6.6. Subjects:
Patients referred to the Joint Warfighter Refractive Surgery Center at WHASC. This population includes active duty members but excludes pregnant women, children (17 and under), military basic trainees, prisoners, and detainees.

3.6.7. Inclusion/Exclusion Criteria:
Inclusion criteria:
Subjects included for this study will be active duty members and DoD beneficiaries referred to the Joint Warfighter Refractive Surgery Center for corrective refractive surgery. This population generally includes healthy individuals 21 years of age and older. Inclusion criteria are:

- M/F ≥21 years of age (PRK is not done on anyone under the age of 21 at this surgery center)
- Have met all criteria for bilateral PRK

Exclusion criteria:

- Patients who do not meet the criteria for refractive surgery
- Patients receiving LASIK
- Patients known to have an allergy to either of the study pain medications
- Patients receiving refractive surgery on only one eye
- Pregnant women, children, military basic trainees, prisoners and detainees
- Subject has used narcotics in the last 6 months

3.6.8. Instrumentation:
A numeric rating scale will be used to survey patient's pain/discomfort level experienced during PRK. The numeric pain scale is an effective pain assessment tool which has shown reliable and valid results in numerous studies for both acute and chronic pain.[3] Its' use is appropriate for discriminating differences in intensity of pain but not in quality of pain. A copy of the pain survey can be found at attachment 4 of the protocol package.

4.0. Human Subject Protection

4.1. Recruitment:
Subject recruitment will occur during the initial pre-operative briefing at the Joint Warfighter Refractive Surgery Center. As standard of care, all persons undergoing refractive surgery are brought together for a group educational meeting regarding refractive surgery. At this meeting subjects who plan on undergoing PRK will be informed of the opportunity to take part in this study. Those interested in participating in the study will be given an informed consent and HIPAA authorization form to take home and review. This will allow at least 24 hours for the patient to discuss the study with friends, relatives, or a physician prior to their surgery. The next day patients who agree to participate in the study will undergo the consent/enrollment process for the study. The PI (who is a resident and will not be the surgeon), an AI, or a research coordinator/assistant will present the information about the study to the prospective subjects. AI's who will also be the surgeon will not recruit any of his/her own patients for the study.

4.2. Consent Processes:
No study specific procedures will be performed without a written and signed informed consent document. If the patient is found eligible and chooses to participate in the study, written informed consent will be obtained by the PI, a non-surgeon AI, or an approved research coordinator/assistant on the day of surgery at the Joint Warfighter Refractive Surgery Center. All aspects of the study will be explained to the subject including any risks and benefits about the study and consent will be obtained only after the subject has had an opportunity to ask questions and discuss the study with the PI, an AI, or assistant. Any subject unable to demonstrate the ability to understand or willingness to sign the informed consent or HIPAA authorization form will be excluded from the study.

4.3 Participation Compensation: Subjects will not be paid for participation in this study.

4.4. Assent Process: N/A

4.5. Benefits:
There is no direct benefit to the patients in the study. This study will only indirectly benefit the patient by contributing to the pool of general medical knowledge which may contribute to future patient care.

4.6. Risks:
As a post-operative pain control study comparing two previously utilized and accepted methods for pain control, there is minimal inherent risk. Patients will receive either one or the other pain medication and will record their perceived pain levels.

With collection of any patient data, there is a risk of inadvertent breach of confidentiality.

To summarize, the risks involved with this study include:
1. Inadvertent breach of confidentiality

4.7. Costs: N/A

4.8. Safeguards for Protecting Information:
Each subject's research record including a copy of the ICD, HIPAA Authorization and the intra-operative pain survey will be stored in a locked cabinet in a locked room. All research data including patient demographics will be kept in a firewall protected electronic database, which will be encrypted, double password protected and the access will be restricted. The research data will be de-identified prior to analysis by the statistician and any links to identifiable data including the Master Key of PII, will be destroyed as soon as possible. There are no planned linkages with external databases, nor is transmission of the data for collaborative use anticipated. The research data will not be utilized for further research activity beyond the protocol stipulations without additional IRB approval.

4.9. Safeguards for Protecting Subjects:
The principal investigator will be responsible for the protocol safety monitoring. The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and over sight staff for confirmation of the study data.

4.9.1. Minimizing Risks:
Patients at the Joint Warfighter Refractive Center have traditionally received acetaminophen/oxycodone but more recently began receiving acetaminophen/codeine for post-operative pain instead and therefore this study would not change the Center's accepted practices except to compare the pain control differences of the these two pain medications.

4.9.2. Vulnerable Populations: N/A

4.9.3. Clinical Care: N/A

4.9.4. Injury Compensation: N/A

4.9.5. Data Safety Monitoring: N/A

5.0. Alternatives: Choosing to have surgery but not to participate in this study is an alternative to volunteering for the study.

6.0. Data Analysis:
The median daily pain scores for first group (codeine + acetaminophen) will be compared to the median pain score of the second group (oxycodone + acetaminophen) using a Wilcoxon signed rank test. Also, median pain scores will be compared between operating physicians and between operating machine (VISX vs Allegretto) using a Wilcoxon signed rank test. In addition, a qualitative analysis will be performed on data obtained. Visual acuities will also be compared between groups if any differences are found in pain scores.

6.1. Outcome Measures:
Post-operative median daily pain scores between two groups using different narcotic medication for pain control.

6.2. Sample size estimation/power analysis:
A power of 0.8 (1-β) was arrived at based on an assumed false negative rate of 0.20 (4 x the assumed false positive rate of 0.05). Effect size of 2/square root of 10 (assumed clinical significance of 2 on a 0-10 numerical pain scale) combined with a false positive rate of 0.05 and a power of 0.8 leads to an N of 41 per group using a two-sided T test or a minimum total number enrolled of 82. Assuming a 18% drop out rate, a total number of 100 patients would make for 45 per group. Based on similar studies showing that only 50% of participants use the narcotic pain control medication, a doubling of the number enrolled should provide for an adequately powered study.

6.3. Statistical Analysis:
Support from the 59 CRD or 59 MDW ST office statistician will be obtained in performing analysis of data.

6.4 Number of Subjects:

Number of subjects planned for WHMC	Enrolled in Study	200	to result in	180	Completing the study.

TOTAL NUMBER OF SUBJECTS (nation-wide/study-wide): 200

7. Duration of Study: Approximate duration of the study: 1.5 years

8. Local and External Support Services: None

9. Intramural (GME) and Extramural Funding Support: None

10. Conflict of Interest: None

11. Use of an Investigational New Drug, use of a Drug for a non-FDA approved purpose, use of an investigative device or use of a placebo:

This research uses an Investigational New Drug **[] YES [x] NO**
This research uses a FDA approved drug for a non-FDA approved purpose **[] YES [x] NO**
This research uses an Investigational Device **[] YES [x] NO**
This research uses a placebo. **[] YES [x] NO**

12. Medical Research Area for the Study: (Pick as many as appropriate)

[] Analytical Chemistry	[] Anatomy	[] Anesthesiology	[] Biochemistry
[] Cardiovascular Surgery	[] Cardiology	[] Cell Biology	[] Dentistry
[] Dermatology	[] Dietetics	[] Electrophysiology	[] Endocrinology
[] Emergency medicine	[] Gastroenterology	[] General Surgery	[] Hematology
[] Histology	[] Immunology/Allergy	[] Infectious Disease	[] Microbiology
[] Molecular Biology	[] Neonatology	[] Neurology	[] Neurosurgery
[] Nursing	[] OB/GYN	[] Occupational Medicine	[] Occupational Therapy
[] Oncology	[x] Ophthalmology	[] Oral/Maxillofacial Surgery	[] Orthopedics
[] Pathology	[] Pediatrics	[] Pharmacology	[] Physical Therapy
[] Mental Health	[] Radiology/Imaging	[] Urology	[] Wellness
[] Other (state):			

13. Attachments:

1. Form A; Certificate of Compliance
2. Informed Consent Document
3. HIPAA Authorization Document
4. Research Questionnaire (Pain Scale)
5. Form A-2; Study Personnel List
6. Form O; Use of a Drug in Research with 2 attachments (Drug Package Inserts)
7. Data Collection Worksheet
8. PII Master Key
9. PI's CITI training certificate
10. PI's CV