CLINICAL TRIAL TO IMPROVE THE MAGNETIC LEVATOR PROSTHESIS NCT03818204

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Clinical Trial to improve the magnetic levator prosthesis (MLP) including the development and testing of a novel adjustable force system

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LIST OF ABBREVIATIONS

MLP	magnetic levator prosthesis
IPF	Interpalpebral fissure
PI	Principal Investigator
VFQ	visual functioning questionnaire
IVI	impact of visual impairment questionnaire
MOCA	Montreal cognitive assessment
NEI	National Eye Institute
NAFL	Sodium Fluoroscein
IRB	Institutional Review Board
MEEI	Massachusetts Eye and Ear Infirmary
HRPP	Human Research Protections Program
MMSE	Mini Mental Status Exam

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with Good Clinical Practices, the U.S. Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), the Code of Federal Regulations applicable to clinical studies (21 CFR 312 – Investigational New Drug Application, 21 CFR 50 – Protection of Human Subjects and 21 CFR 54. The Principal Investigator at the study site Massachusetts Eye and Ear Infirmary will assure that no deviation from, or changes to the protocol will take place without prior agreement documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

PROTOCOL SUMMARY

Title:	Clinical Trial to improve the magnetic levator prosthesis (MLP) including the development and testing of a novel adjustable force system
Objectives:	To improve the magnetic levator prosthesis (MLP) by development and testing of a novel adjustable force system.
Endpoints	1. Completion of the 2 visit protocol with acquisition of interpalpebral fissue height during resting open without the MLP, and with the MLP over 5 adjustable force levels.

Population:	Individuals with severe unilateral or bilateral ptosis (n = 19) defined as occlusion of the lower pupil margin by the lid in the resting state
Phase:	I/II
Number of Sites enrolling participants:	1
Description of Study Agent :	magnetic levator prosthesis (MLP) with compatible spectacle frames
Study Duration:	2 to 3 years
Participant Duration:	2 visits over 2 weeks.

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1 KEY ROLES

Principal Investigator – Overall responsibility for all study related activities.

Post Doctoral Fellow- Responsible for consenting, enrolling and scheduling subjects. Also will collect, record and report all study data.

Reseach Technician 1 – Responsible for 3-D design and printing of prototypes.

Research Technician 2 – Responsible for producing the MLP lid magnet array. Also responsible for randomization and counterbalancing schemes.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Blepharoptosis, defined as incomplete opening of the upper eyelid, occurs due to abnormalities in the function or structure of the levator palpebrae superioris muscle, injury to or dysfunction of the superior division of the 3rd cranial nerve, or structural abnormalities.[1] Etiologies include congenital abnormalities, stroke, traumatic brain injury, tumors of the brain or face, viral illnesses, diabetes, autoimmune disorders such as myasthenia gravis, and general aging mechanisms.[1] The prevalence of blepharoptosis within the US general population is unknown; however, in Korean and U.K. general population it has been reported to be 11% [2, 3] suggesting **30 million people in the U.S.** have the disorder.

Severe ptosis and associated ophthalmoplegia cause low vision with negative effects on function and quality of life – Total bilateral ptosis causes profound yet potentially reversible visual impairment. Associated ophthalmoplegia results in an inability to consistently utilize the fovea, and so in many cases

magnification is useful. In bilateral 3rd nerve palsy, for example, the eye is frequently permanently abducted 30° or more, so even if the lids are opened common low vision rehabilitation interventions are needed. A similar but usually less severe situation exists in poorly controlled myasthenia gravis. When ptosis is subtotal but severe, patients are symptomatic of constricted visual field reporting problems with mobility and inability to drive. Inability to drive and effort of constant frontalis recruitment limits employability, making travel to work and sustained computer viewing very difficult. Severe unilateral ptosis (CN III palsy) causes loss of binocular peripheral field (~30°), stereopsis, and binocular summation (which is often problematic at night or other dim environments). All levels of ptosis have negative social and cosmetic impacts which are likely to affect employment and social well-being.

Common surgical treatments - The most common method currently used to correct ptosis involves surgical tightening of the levator muscle, or in more severe cases, frontalis sling.[1] While these procedures are a mainstay of treatment, in our experience they have disadvantages in that they do not always restore normal blink function and over-correction may result in exposure keratitis. In severe cases of ptosis a conservative approach is needed leaving the ptosis under-corrected, and so even surgical candidates may benefit from magnetic correction.

An effective easily adjustable and/or non-surgical treatment is needed - Substantially less attention has been given to non-surgical approaches for ptosis, which has led to lack of effective options during the early recovery period from neurological etiologies, in cases with daily variability in the ptosis such as Myasthenia Gravis, or other cases where surgery is contraindicated. Ability for the patient to easily adjust the correction as the ptosis varies would be advantageous whether it were applied surgically or not.

Limitations of available temporary treatments - We believe that available temporary or non-surgical treatments are ineffective and even contraindicated for many target populations. These include taping the lid(s) open and propping the lid open with a wire on the glasses (ptosis crutch).[4] Unfortunately there is a paucity of data on safety or efficacy of the ptosis crutch or taping. The crutch has to be continually adjusted to keep the lid elevated, does not allow a complete blink,[5] and poses a risk for ocular injury during adjustment or should the patient fall. We have frequently encountered use of skin tape to elevate the eye lid, but this has potentially damaging effects on the ocular surface from incomplete eye closure.

Static magnets could provide force to elevate the eyelid while still allowing eye closure - In most types of ptosis, while opening of the eyelid is impaired, the neuromuscular complex for eye closure (Orbicularis oculi muscle/cranial nerve (CN) VII) is intact. [1] In these cases the ptosis might be alleviated using a permanent static magnet system to provide the force to elevate the upper eyelid.[6] The static force exerted by the permanent magnet to open the eyelid should be easily overcome by the Orbicularis Oculi muscle, assuming the force of the magnet is not too great, reanimating the blink. This approach utilizes well-understood, widely available and inexpensive static magnetic materials. Electromagnets

might seem like an attractive option for the ability to modulate force; however, they generate heat and would consume too much energy to be feasible for continuous use. We had also considered electrical stimulation of the levator muscle; however, our mentors who have investigated the possibility of this approach previously indicated that repeated stimulation externally on the skin is painful in addition to difficulty accessing the levator non-surgically via this technique.

Prior attempts to use magnets for ptosis - The concept of correcting ptosis with magnetic force was first presented in the 1970's.[6] Conway described attaching Mu-metal 13 x 4 x 0.5 mm to the upper lid in 3 patients (attached with eyelash adhesive or blenderm tape), and a small bar magnet to the spectacles. Specifications of the ferrite spectacle magnet were not provided; however, we measured them in the photos to be ~20 x 5 x 10mm. Conway's photographs showed elevation of the eyelid when the lid and spectacle magnet were in contact; however, the ferrite magnet/Mu-metal would not have generated enough force to elevate the lid from the closed position, where there is typically 15 to 20mm separation.[5] As a result the magnet glasses would have needed frequent adjustment to bring the materials back into direct contact after each blink offering no substantial benefit over the long available ptosis crutch. It is therefore not surprising that the treatment was never commercialized. Since Conway's report, we find no publications on the use of magnets for ptosis, although they have been attempted for lagophthalmos via surgical implantation with only limited success.[7-10] Problems related to surgical implantation highlight the benefit of first refining the approach non-surgically. Static magnets are also better suited for ptosis as compared to lagophthalmos, because of the relative strength of the orbicularis compared to the levator.

2.2 RATIONALE

We recently described a novel non-surgical magnetic eyewear device referred to as the Magnetic Levator Prosthesis (MLP) that restored blinking in patients with severe paralytic ptosis.[5, 17-19] The force to lift the lid was produced by a static Neodymium magnet embedded in a glasses frame and a polymer embedded (PDMS) micro-magnet array fitted externally to the upper lid with Tegaderm IV securement film (Fig 1). The Tegaderm is FDA approved for extended wear on the skin and even as an eye covering. It generated a strong bond, keeping the magnetic array affixed to the eye lid skin for a mean of 6 ± 4 days with good patient reported comfort when used for 2 hours per day during rehabilitation therapies.

Translational Promise – This proposed research to further improve the approach and confirm safety, feasibility, and relative efficacy for chronic management of ptosis is needed prior to commercialization. The aims of the proposed study target the clinical population of the PI who specializes in low vision rehabilitation with subspecialty in neurological visual impairments. This is a large and underserved patient population which includes many individuals with recent neurological pathology, many of whom

are residing in inpatient rehabilitation facilities (IRF). IRFs provide 24 hour medical supervision and rehabilitation therapies to patients who are medically stable and are able to participate in a minimum of 3 hours/day of therapy. There are 1,165 IRFs in the U.S.[20] with an average length of stay of 16 days.[21] If we conservatively estimate an average of 50 beds per 1,165 IRFs revolving every 16 days there should be approximately 1.2 million admissions and discharges per year in IRFs nationwide. Of that population, ~32% are recovering from stroke and 6% from traumatic brain injury.[21] Prevalence of CN III palsy in stroke populations has been reported at 2.5%,[22] and 4.4% in TBI (internal data). Therefore, the estimated national target population for temporary management of severe ptosis in IRFs alone is 12,000 patients annually. In our IRF, internal review found a rate of 24 cases of severe ptosis in 2015-2016. No one stands to directly and immediately benefit more from this technology than patients with severe bilateral ptosis. While this is presumed to be a rare situation we have encountered 8 such patients in the past 2 years without any active recruiting effort. We have also encountered multiple patients with severe unilateral ptosis obscuring the vision in their better eye for whom surgery was contraindicated. There is no available option for these patients other than taping the lids open or the ptosis crutch with the aforementioned problems with these approaches.

Scientific Premise: In summary, premise for the proposed work is that ptosis is a major public health concern which to this point has received less attention than it's lagophthalmos counterpart despite the fact that it causes similar discomfort and disability (but without the extreme consequence of exposure and scarring). Better non-surgical options are needed. Weaknesses in prior work in the field concerning magnetic correction included use of ferrite magnets, inadequate adhesion methods for external placement, moving too soon to surgical implantation, and lack of evidence from randomized controlled trials to guide clinical approaches. We will fill a significant gap in the field in terms of non-surgical correction while not excluding use of data and methodology to advance success with surgical implantation.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Risk 1: Dryness or sorness in the eye or on the lid skin from prolonged use of the MLP has been reported a prior study of the MLP (Singh et. al 2016). In that study (n = 6), *"total usage time was 32 weeks, 3 weeks, 1 week, 8 weeks, 2 weeks, and 2 weeks, in each patient respectively. The average wear time of the device was 5 (±2) hrs/d. Patients 1,2,4,5-6 continued to use the device at the end of the study period while P3 recovered negating further need. There were no adverse events (as predefined). Mild (2/10) skin irritation and worsening in superficial inferior corneal staining (from 0 to 2) occurred in P1's*

first week after 8 hrs/d of wear. Reducing wear time to 4 hrs/d and starting artificial tears every 4 hrs reversed SPK & prevented further complications."

Singh NK, Paschalis EI, Tomasi M, Rizzo JF, Houston KE. The boston blink-netic project: preliminary outpatient feasibility results (abstract). Optom Vis Sci 2016;93: E-abstract 16118.

There have not been any cases of irreversible damage to the ocular surface occurring during use of the MLP and this would be extremely unlikely because the MLP is easily disengaged by removing the glasses and the lid magnet is easily removed with nylon tweezers. We include the remote possibility of irreversible effects of extended exposure in the consent materials, which is meant to refer to any permanent ocular surface manifestation that may result from exposure ranging from minor dry sensation to scarring of the cornea.

Risk 2, reduced blink reflex: If the fitting of the MLP is not ideal, it is possible that participants (children and adults) would experience slowed or incomplete blink reflex. There is the potential that this could cause reversible ocular surface drying and discomfort. Participants, parents, and involved caregivers will be given specific instruction on how identify problems and when to remove the MLP. To summarize, they will be instructed to ask themselves at regular intervals "what is my level of comfort on a scale of 1-10" and if it is lower than 5 to remove the MLP and contact the study staff to schedule a visit to investigate.

IT IS ALSO POSSIBLE THAT A REDUCED BLINK REFLEX COULD ELEVATE THE RISK OF FOREIGN BODY IN THE CASE OF PROJECTILES. ALL PARTICIPANTS WILL BE FITTED WITH SAFETY GRADE OR POLYCARBONATE LENSES, IN THEIR PRESCRIPTION (OR NON-PRESCRIPTION PLANO IF THEY REQUIRE NONE). PARTICIPANTS WILL BE INSTRUCTED TO WEAR ADDITIONAL PROTECTIVE EYEWEAR AND TO AVOID PLACES LIKE MACHINE SHOPS WHERE THERE COULD BE METAL SHAVINGS. THE LID MAGNETS ARE NOT STRONG ENOUGH TO PROPEL A MAGNETIC/METAL OBJECT TOWARDS THE EYE AND THE MAGNETS SHOULD ACTUALLY REDUCE THE RISK FOR METALLIC FOREIGN BODY PROJECTILE ENTERING THE EYE BY REDIRECTING IT TOWARDS THE SPECTACLE MAGNET; HOWEVER, THERE IS RISK THAT METAL SHAVINGS COULD ACCUMULATE AROUND THE MAGNETS IF THE DEVICE IS USED IN A SITUATION SUCH AS A WORKSHOP WHERE SHAVINGS ARE PRESENT. WHILE THESE WOULD NOT BE PROJECTED INTO THE EYE, MINOR INJURY MAY RESULT IF THE SHAVINGS GET AROUND THE EYE AND THEN ARE RUBBED INTO OR SPRINKLE INTO THE EYE(S). STANDARD SAFETY GOGGLES WILL FIT OVER THE SPECTACLES AND PARTICIPANTS WILL BE INFORMED THAT THEY SHOULD BE WORN AS THEY NORMALLY WOULD. 2.3.2

KNOWN POTENTIAL BENEFITS

Possible treatment for restoration of eyelid motility in subjects who wear the device comfortably.

3 OBJECTIVES AND PURPOSE

To improve the magnetic levator prosthesis (MLP) by development and testing of a novel adjustable force system. If endpoints are met and the device is determined to be feasible the study will continue to a randomized clinical trial comparing the MLP against the predicate treatment of taping the lids (future IRB application).

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

A blinded study to perform measurements and experiments to improve the magnetic levator prosthesis (MLP) including the development and testing of a novel adjustable force system.

4.2.1 PRIMARY ENDPOINTS

Completion of the 2 visit protocol with acquisition of interpalpebral fissue height during resting open without the MLP, and with the MLP over 5 adjustable force levels.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

1. Presence of Blepharoptosis for at least one eye which occludes the visual axis in the resting state (no frontalis drive), 2. Moderate cognitive function or better defined as greater than or equal to 18 out of 30 on a pre-screening of the Mini-Mental State Exam. 3. Age 5 or older.

5.2 PARTICIPANT EXCLUSION CRITERIA

1. Absence of ptosis which occludes the visual axis or presence of a corneal ulcer of any size. 2. Age less than 5, Severe Cognitive impairment defined as MMSE score <18, behaviors consistent with delirium (combinations of disorientation, hallucinations, delusions, and incoherent speech), or lethargy.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

The aims of the proposed study target the clinical population of the PI who specializes in low vision rehabilitation with subspecialty in neurological visual impairments.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Subjects have a right to withdraw from the study at any time. Additionally, the subject may be withdrawn from the study for any reasons: if it is in the best interest of the subject, intercurrent illness, adverse events, or worsening condition. The site investigators may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

Reasons for subject discontinuation may include, but are not limited to, the following:

- Investigator determination that it is not in the best interest of the subject to continue participation
- Serious adverse events
- Any other safety concerns

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

If a participant needs to withdraw early, they will be asked to accept a final telephone call at the end of the study to confirm vital status. Participants who are withdrawn due to an adverse event, serious or not, will be followed until the resolution of the event.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

If the study is terminated or suspended prematurely, all enrolled participants will be notified and asked to attend a final safety visit. If there are participants with ongoing adverse events at the time of premature termination those participants will be followed until resolution of the event.

6 STUDY DEVICE

6.1 STUDY DEVICE DESCRIPTION

Neodymium magnet embedded in a glasses frame and a polymer embedded (PDMS) micro-magnet array fitted externally to the upper lid with IV 3000 securement film. The IV 3000 is FDA approved for extended wear on the skin. Tegaderm, which is essentially the same adhesive, is even FDA approved as an eye covering (we used Tegaderm in early studies but switched to IV 3000 for its superior ease of handling based on packaging technique). It generates a strong bond, in a prior study keeping the magnetic array affixed to the eye lid skin for a mean of 6 ± 4 days with good participant reported comfort when used for 2 hours per day during rehabilitation therapies. In order to allow doctors and patients to easily adjust the force of the MLP in the interest of maximizing their comfort and blink

quality while accommodating variability in ptosis or lid magnet positioning, we propose to further develop and test a novel approach where the force is adjusted by manually rotating the spectacle magnet with a small dial on the side of the spectacle frame. The MLP is FDA exempt as a Class 1 Device. An Investigational Device Exemption (IDE) application was not required in prior studies approved by the MEEI IRB HSC and should not be required in order to carry out this study. MLP status as a device was reviewed extensively by Leila Foster and her team as well as by legal (Maureen Kelley), last reviewed in fall 2017.

6.1.1 ACQUISITION

Magnets will be acquired from SM Magnetics, Pelham AL or similar supplier. PDMS supplies will be acquired from Fisher Scientific. Frame supplies will be acquired from Designs For Vision Rokokam, NY , Michelle Moretti Eyeware and Skelmet, Boston MA.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Arrays will be labeled with lot and batch numbers.

6.1.3 PRODUCT STORAGE AND STABILITY

Only the arrays have an expiration date. Neodymium magnets are highly stable and resistant to demagnetization. The spectacle magnets will have an expiration of 5 years. The PDMS arrays will have an expiration of 1 year. They are stored at room temperature.

6.1.4 PREPARATION

Magnets are prepared by the manufacturer and coated in nickel. They will be embedded in PDMS at Schepens Eye Research Institute using a mold produced onsite with a 3-D printer.

6.1.9 DURATION OF THERAPY

see other sections

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

The MLP is FDA exempt as a Class 1 Device and therefore an Investigational Device Exemption (IDE) application was not required in prior studies approved by the MEEI IRB HSC and should not required in order to carry out this study. MLP status as a device was reviewed extensively in the fall of 2017 by Leila Foster and her team as well as by legal (Maureen Kelley). Mass Eye and Ear has submitted a patent application for the technology, and so status was also reviewed by Ojas Mehta and his team in the Intellectual Property department.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The devices will be stored and dispensed from the lab offices at Schepens Eye Institute. Logs will be keep by the Research Assitant to keep account of which devices where used for the specific subjects. If devices are returned that will also be noted on the device logs.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

A cognitive pre-screening to guide the consent process will be administered as described in section 13.3.2. After consent, participants will have their acuity measured (refraction as needed), slit lamp with Nafl & NEI scale. Next, the MLP will be placed on the patient and video recordings made for 1 minute (comfort monitored with a 10-point scale during this period). Next, the effect of force adjustment via magnet rotation on lid position will be measured. The spectacle magnet will be rotated (settings labeled 1-4, counterbalanced), and videos recorded for another minute at each rotational increment. For video recording we will have 2 cameras: 1 straight on and the other angled up (to capture upper lid apposition to globe, Fig 5d&e). Recording will be done with a blue filter and NaFl to simultaneously document tear film. Additional NaFl will be added over the trial at the clinical staff discretion as needed. Once optimal rotational increment is found, a 20 minute trial at that setting will be performed with repeat of video recording with comfort and efficacy scale. Afterwards, the array will be removed and an array with the alternative polarization will be applied. We will then record for 1 min getting comfort and efficacy data and repeating the rotation experiment followed by another 20-minute trial. At the end of the study visit we will repeat visual acuity, slit lamp with Nafl & NEI cornea scale, and video recordings with comfort scale will be repeated. As this is a fitting and optimization process, it is possible that additional visits will be necessary in order to make modifications, but these will be optional.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Pre-Screening: In order to guide the consent/assent process, the approved study staff will administer a pre-consent cognitive screening using the Mini-Mental State Exam (MMSE). If score is 18-23 (maximum of 30) representing mild cognitive impairment (Tomburgh et al 1992), candidates will be asked return with a caregiver (if one is not present). If score is <18, they will not be eligible. Screening/Study Intake: Participants will have their acuity measured (refraction as needed), slit lamp with Nafl & NEI scale. Inclusion Criteria: Presence of Blepharoptosis for at least one eye which occludes the visual axis in the resting state (no frontalis drive), moderate cognitive function or better defined as greater than or equal to 18 out of 30 on a pre-screening of the Mini-Mental State Exam, age 5 or older. Exclusion Criteria: Absence of ptosis which occludes the visual axis or presence of a corneal ulcer of any size. Age less than 5, Severe Cognitive impairment defined as MMSE score <18, behaviors consistent with delirium (combinations of disorientation, hallucinations, delusions, and incoherent speech), or lethargy. These individuals must be excluded since participation requires competent self-care, reliable responses and

cooperation during fitting of the device. Children need to be included because they represent an important target population (pediatric neuro-muscular conditions), and because facial structure and skin characteristics may result in a different response than adults

7.3.2 Enrollment/Baseline
See 7.1.1 above7.3.3

7.3.3 Follow-up

See 7.1.1 above

7.3.4 FINAL STUDY VISIT

At the final study visit a clinical decision will be made as to whether or not the MLP is recommended for continued use, and which version of the device was best. Because the MLP is not regulated by the FDA as a spectacle device (similar to low vision aids), and because there is no comparable alternative for non-surgical management, participant will be allowed to take the MLP and continue wearing it, and transferred to the clinical practice of the PI.

7.3.5 EARLY TERMINATION VISIT

In the event a participant is terminated from the study due to an Adverse Event, the study PI will follow the participant for at least 30 days after termination to confirm the event has resolved or the patient is receiving appropriate treatment.

7.3.7 SCHEDULE OF EVENTS TABLE

Procedures	VISIT 1 (ASSESSMENTS WILL BE REPEATED IF PARTICIPANT AGREES)	Visit 2 (1 week +/-2 days Visit 1 assessments will be repeated if participatne agrees and and the clinical staff will determine if this is clinically appropriate
Follow Up Phone Call		X
Visual Acuity (refraction if needed)	X	X
Slit Lamp Exam	X	X
NEI corneal staining scale	X	X
Baseline Video Recording	X	X
Eye Lid Prep	X	

Procedures	VISIT 1 (ASSESSMENTS WILL BE REPEATED IF PARTICIPANT AGREES)	Visit 2 (1 week +/-2 days Visit 1 assessments will be repeated if participatne agrees and and the clinical staff will determine if this is clinically appropriate
Measurement of force to open the ptotic lid	X	
Polarity experiment, case 1 (apply lid magnet array)	X	
Video recording	X	X
10 point comfort and efficacy scale	X	X
spectacle magnet rotation experiment	X	
20 minute trial at optimum rotation	X	
Repeat Video Recording	X	
Repeat 10 point comfort and efficacy scale	X	
Polarity experiment, case 2 (apply lid magnet array)	X	
spectacle magnet rotation experiment	X	
20 minute trial at optimum rotation	X	
Video recording	X	
10 Point Comfort and Efficacy Scale		X
Repeat visual acuity	X	
Repeat Slit Lamp Exam	X	
Repeat NEI Nafl scale	X	
Clinical Decision		X

<Insert text>

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Oral and ophthalmic concomitant medications will be reviewed and recorded to confirm the patient does not have any systemic disease that would interfere with the study assessments and or data.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

none

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Ophthalmic ointment or skin ointment applied near the eyes interferes with adhesion of the lid magnet and will need to be discontinued at least 1 day prior to the study. Patients may continue with artificial tears.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Because the MLP is not regulated by the FDA as a spectacle device (similar to low vision aids), and because there is no comparable alternative for non-surgical management, participants will be allowed to take the MLP and continue wearing it after completion of the study. MEEI has already approved provision of the MLP to non-research subject patients under the Humanitarian Devices rules.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

The safety of the study device will be evaluated at every visit following the enrollment visit and will be defined by the incidence of related adverse events. Specifically, we will evaluate:

- **Systemic safety**: Incidence and severity of systemic adverse events during the study (adverse events spontaneously reported or observed by the Research Assistant).
- **Ocular safety**: Incidence and severity of ocular adverse events during the study (ophthalmic examination, adverse events spontaneously reported).
- **SAFETY CUTOFFS: Should visual acuity decrease more than 2 lines, worsening of corneal rating of more than 1.5 points or other ocular surface ratings more than 2 points, and comfort rating lower than 5/10; study activities will cease for at least 1 week and an adverse event report to the IRB. Serious adverse events which will result in immediate dismissal from the study (and treatment) include: 1) development of a corneal epithelial defect or infiltrate without epithelial defect or 2) broken skin on the eyelid.**

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious Adverse Event (SAE): Any event temporally associated with the subject's participation in research that meets any of the following criteria:

- Results in death
- Is life threatening
- Requires hospitalization/prolongation of hospitalization
- Results in congenital anomaly
- Results in persistent or significant disability/incapacity
- Required intervention to prevent permanent impairment/damage

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Any incident, experience, or outcome (including data loss) that is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures described in the protocol and the characteristics of the subject population being studied. Unanticipated problems may include protocol deviations that are not adverse events

8.2 CLASSIFICATION OF AN ADVERSE EVENT

The Investigator will promptly review documented adverse events and abnormal findings to determine 1) if the abnormal finding should be classified as an adverse event: 2) if there is a reasonable possibility that the adverse event was caused by the study device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

8.2.2 RELATIONSHIP TO STUDY DEVICE

If an adverse event or serious adverse event is recorded the study PI will determine the relationship to the study device.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events or abnormal findings thought to be associated with the study device will be followed until the event (or its sequel) or the abnormal finding resolves or stabilizes at a level acceptable to the Investigator. Events that have not resolved or stabilized will be followed for 30 days post study completion. Subjects will be encouraged to follow up with their physician for the treatment of any events beyond 30 days post study completion.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All adverse events will be reviewed by the principal investigator within 24 hours of notification and reported to the Mass Eye and Ear IRB on the following schedule:

- Possibly, Probably, or Definitely Related Expected AE – Report to IRB on annual basis
- Possibly, Probably, or Definitely Related Expected Serious AE – Report to IRB on annual basis
- Possibly, Probably, or Definitely Related Unexpected AE – Report to IRB within 30 days of event
- Possibly, Probably, or Definitely Related Unanticipated Problem – Report to IRB within 7 days of event (24 hours for death of data loss)
- Possibly, Probably, or Definitely Related Unexpected Serious AE – Report to IRB within 7 days of event

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Any adverse events that are serious, unexpected and related or possibly related to the study will be reported to the Mass Eye and Ear IRB within 7 calendar days from the time the PI becomes aware of the event.

Any unexpected and study-related death will be reported to the Mass Eye and Ear IRB within 24 hours of the PI's knowledge of the event by e-mail or telephone.

8.4.3 UNANTICIPATED PROBLEM REPORTING

All UAPs involving risks to subjects or others will be reported in writing to the Mass Eye and Ear IRB within 7 calendar days from the time the PI becomes aware of the event. If a UAP or an unexpected SAE results in a subject's death or was potentially life-threatening, the PI will notify the Mass Eye and Ear IRB through e-mail or phone within 24 hours from the time the event is identified. A follow-up report will be submitted if applicable, at a later date when more information is available. For UAPs that result in data loss the PI will notify the Mass Eye and Ear IRB through e-mail or phone within 24 hours from the time the UAP is identified.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

Statistical Analysis:

Primary Outcome: The effect of angular position on interpalpebral fissure during the resting open phase will be modeled using linear mixed-effects (multiple regression) models. The five angular (rotation) angles will be randomly mapped over the arbitrary labels of 1 to 5 to mask the participant and study staff and treated as categorical variables. Because repeated measurements will be performed on each eye and each participant might respond differently to each angular position, participant and angular position within participant-eye will be included as random effects. Demographic covariates, such as age and gender, will be evaluated to determine if they have a meaningful effect on interpalpebral fissure or comfort.

Sample Size Calculation: Data was originally not available to perform a sample size calculation for the mixed effects analysis. Instead we categorized the data for success versus failure defined as a clinically meaningful change of >1mm in interpalpebral fissure across the range of rotation forces. Based on this it was estimated that with 30 subjects we will have 80% power to show that the success rate significantly exceeds 50% with a one-sided alpha=0.025 exact binomial test of one proportion if the true success rate is 75% or greater. Therefore we originally aimed to enroll 30 subjects. Interim analysis was conducted after 11 subjects were enrolled and sample size calculation was adjusted down to 19 subjects.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Linear mixed-effects will be used for the primary outcome.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Analyses will be performed by the study staff using statistical software (STATA 14 or similar). Primary outcome is the change in interpalpebral fissure with versus without MLP, and change in interpalpebral fissure across the 5 rotation angles.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The effect of the five angular (rotation) angles on interpalpebral fissure during the spontaneous blink will be modeled using linear mixed-effects model, identical to that described for the primary outcome. Dependent variable will be the measured interpalpebral fissure during the 3 minima of each spontaneous blink event.

The effect of MLP compared to baseline without device will be modeled with another linear mixed effects model.

To model comfort level, we will treat the reported Likert-type data as interval data and use a linear mixed-effect model with angular position number as the fixed effect and participant and angular position number within participant-eye as random effects.

To statistically determine whether there are between-participant differences in response to angular position, we will employ profile analysis which is a multivariate statistical technique that uses multiple analyses of variance for repeated measures to test piecewise parallelism.

10.4.4 SAFETY ANALYSES

Clinical study staff will acquire high resolution magnified images of the ocular surface and eyelid skin which will bereviewed by the PI and his study team weekly during project meetings. On-site monitoring of participant safety will be utilized by the PI or other study personnel. This is appropriate since problems can be immediately detected and addressed by research staff experienced in examination of the eye. A monitoring log of expected and unexpected events will be kept. Events will be documented on paper and sent to the PI (if he is not the one examining the participant) who will place a follow-up call to the participant that day and the next day as needed. Paper documentation will be kept in the study binder and then transferred to a worksheet in the study master spreadsheet. Non-compliance with protocol (e.g. failure to use the study checklist or properly document or report in a timely manner adverse events) will be documented. Once identified, minor issues will be addressed by the PI by special meeting or at weekly study meetings. Special meetings will be called depending on the seriousness of the issue. Repeated offenses will result in removal of that study staff from the protocol. Adverse events will be documented and reported to the IRB and NEI per protocol.

10.4.5 ADHERENCE AND RETENTION ANALYSES

DATA SUMMARIES WILL BE PRODUCED (INCLUDING DATA ON SUBJECT ENROLLMENT, WITHDRAWALS, PRIMARY OUTCOME MEASURES, AND ANY SAFETY ISSUES) ON A PERIODIC BASIS AND REVIEWED BY THE PI AND OTHER STUDY PERSONNEL.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

10.4.7 PLANNED INTERIM ANALYSES

Conduct after 11 subjects are enrolled.

10.4.7.1 SAFETY REVIEW

The summaries will be reviewed by an internal committee comprising the PI and members of the research team to monitor data quality, study progress and determine whether the study should change in any way or be stopped. Serious (expected or unexpected) adverse events will be reported immediately to the PI (by a subject or member of the research team).

Minor adverse events (e.g. mild discomfort of the lids) will be recorded on a subject's data sheet at the time of occurrence; they will subsequently be reported internally for that study. Minor adverse events will also be reported on an annual basis to the relevant IRB committees, as part of the annual IRB review of each approved study.

10.4.7.2 EFFICACY REVIEW

Preliminary data analyses will occur periodically.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Subgroup analysis is not part of the analysis plan

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

P-values used to indicate significance will be corrected where appropriate.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Individual response data will be recorded on data sheets and input into Excel spreadsheets.

10.4.11 EXPLORATORY ANALYSES

No exploratory analyses are planned.

10.5 SAMPLE SIZE

19 subjects will be enrolled into this study.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 MASKING PROCEDURES

Only masked/blinded clinical staff will apply the lid magnets polarized either through thickness or through height (counterbalanced) to the study subjects.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

The PI will determine if for safety reasons, the study staff needs to be unblinded on a subject by subject basis and/or during a specific study visit

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Data collection sheets will be completed for each subject enrolled into the clinical study. Data Collection sheets will be study visit specific and the PI will review, approve and sign/date each subject visit. Investigator's signature or record locking serving as attestation of the responsibility for ensuring that all clinical data entered on the data collection sheets are complete, accurate and authentic.

All computer generated data will be stored on internal MEEI servers located on encrypted, password protected MEEI computers. Only the PI and researchers specific to this study who have been granted access to the data by the PI will be able to view the data in the MEEI network protected folder. If data is sent out to be analyzed the data will be de-identified. The data will contain subject identification numbers, which are linked to identifiers on a separately secured spreadsheet. The data will be coded by assigning each participant a subject identification number and removing any identifiable information. The code will be secured by the PI and Study staff in the drive located on encrypted, password protected computers at Schepens. The code that links information that can identify the participant to the data collected for this research will be kept separate from their health information, which will be destroyed once this study is complete and the manuscript has been published.

12 QUALITY ASSURANCE AND QUALITY CONTROL

The Principal Investigator will be responsible for quality assurance during this study. The Principal Investigator will confirm that the study device is stored correctly. The Principle Investigator will also train study staff on the protocol procedures and will confirm staff can confidently complete the study related assessments.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

All staff designated to work on this trial will have CITI certification for confirmation of GCP training and their CV's, licenses and other forms of certifications related to conducting research will be kept with the study regulatory binder.

13.2 INSTITUTIONAL REVIEW BOARD

The IRB of record for this study will be the MEEI review board, The Human Research Protections Program. The protocol will be approved by the HRPP office prior to subject enrollment and will be reviewed yearly after initial approval. Any adverse events or serious adverse events will be reported to the HRPP office; however this is not expected to occur because this is a minimal risk protocol.

13.3 INFORMED CONSENT PROCESS

Subjects are required to sign an informed consent before participating in the study. The consent will be signed in front of a study member (witness). The witness and investigator will sign and date the consent form. A note will be made on the study record that the informed consent was signed by the participant. The informed consent will follow the guidelines set by the MEEI IRB. A copy of the consent form will be given to the participant. A member of the study team will review the study procedures, visit schedule, risk and benefits, alternative treatments and rights to withdraw and ask questions with all potential subjects before signing the consent. Every participant has a right to withdraw at any time from the study without affecting their care or relationship with the treating physician and participating institution. The financial responsibilities of the participant will be discussed. All participants are required to sign a Health Insurance Portability and Accountability Act (HIPAA) form before participating (unless this is combined with the consent). A study member will explain and discuss with the participant their confidentiality rights as described in the HIPAA form.

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Participants who are determined by their clinical specialist to have Blepharoptosis will receive a recruitment packet from the services' administrative assistant. If subjects are identified by a pre-screening (i.e. chart is prescreened and tagged by the clinical research office) and they are interested in the study they will schedule another appointment in the SERI vision rehab lab at 20 Staniford st. The scheduler/study coordinator/research assistant will inquire about any prior diagnosis of dementia or significant cognitive impairment, and if so coordinate the primary caregiver to also attend the visit. Pre-

Screening: Approved study staff will administer a short cognitive pre-screening (mini-mental state exam, MMSE) to determine if there is any cognitive impairment. The MMSE will not be linked to a study identifier and will be retained for aggregate analysis only. If score is <18, the individual is not eligible. If score is 18-23, an assent process will occur, and consent obtained from the primary caregiver (the health care proxy (if one has been named), or the spouse or family member (in that order of preference)). If the study candidate is a child, one parent will sign the consent and children under 14 will sign the assent and children over 14 and older will sign the consent (unless decisionally impaired as determined with the same MMSE criteria). Dr. Houston, the PI, has approximately 5 years experience in providing informed consent to patients with neurological disorders, and >10 years providing eye care for this population. He will perform the informed consent in a private room at Schepens Eye Research Institute. The study will be explained to the potential participant and they will be asked to read (or have read to them) and sign the approved informed consent (or assent) form before participation in the study. Alternatives to participating will be explained. They will be given ample opportunity to discuss all aspects of the study before signing the form. A detailed explanation of the interventions and how they work will be given, including showing them the device and allowing them to ask questions. Dr. Houston will leave the room allowing the prospective participant and any family members to discuss in private. Prospective participants will be specifically offered the opportunity to discuss the interventions and the study with Dr. Houston, their ophthalmologist, and family members/caregivers prior to consenting. A copy of the consent form will be given to the participant.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Safeguards will be employed to protect the confidentiality of participant data including the following: Each member of the study team has completed privacy training and information security training at Mass Eye and Ear, paper files will be locked in cabinets when not in use, paper files will be protected from inappropriate access when in use, mobile computing devices and storage media will be locked in cabinets when not in use, computing devices will be protected from inappropriate access when in use, research data will be coded using a study identification number that does not include the participant's initials and is not derived from the participant's identifiable information, the key linking the study ID to the participant's info is available only to the study team, the key will be stored in a locked password protected network with access limited to the study members who require access to this information, electronic data will be stored on folders only available to the study team. Devices for video recording components of the study will be encrypted and/or password protected where possible and data will be promptly transferred and deleted from the device. All video/image and other data will be de-identified prior to publication. We will attempt to capture video/image data so as to only include the eyes, which will therefore not be identifiable. In situations where this is not possible (ie participant moves), video/image data will be cropped to reduce the image to eliminate other facial features. Audio will ultimately be removed from the video files, but may be needed during processing to determine if blinks are reflexive or the experimenter has asked the participant to volitionally blink. De-identified cropped videos with sound removed will be published as supplementary data or on a public site such as YouTube, and will be used in lectures presenting results of the work. Participants will be informed that their de-identified video recordings may be shared in this manner and ask to check a box on the consent form. Those who decline will not be excluded from participation and this will be emphasized in the consent form and verbally by the PI during the consent process.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data management and collection will be monitored by the PI. Study staff involved in data collection will maintain all training and certifications required by the MEEI/IRB. Paper data forms will be stored in a locked file cabinet in or near the PI's office at Schepens Eye Research Institute, 20 Staniford St. Boston MA, 02114.

14.2 STUDY RECORDS RETENTION

IDENTIFIERS WILL BE DESTROYED AFTER PUBLICATION OF THE RESULTS. THE PROJECTED TIME FRAME IS 3 YEARS FROM THE BEGINNING OF THE STUDY. STUDY RECORDS IN DEIDENIFIED FORM WILL BE KEPT INDEFINITELY.

14.3 PROTOCOL DEVIATIONS

Protocol deviations and unanticipated problems will be reported to the IRB upon knowledge of the occurrence. Reporting of deviations and problems will be done following the MEEI HRPP office policy.

14.4 PUBLICATION AND DATA SHARING POLICY

Study results will be published at scientific conferences and peer-reviewed journals. Study participants will not be identifiable by the data presented within the publications.

16 CONFLICT OF INTEREST POLICY

Per MEEI Human Protection Program policy, the Principal Investigator and Sub Investigators will complete the MEEI IRB Conflict of Interest In Research Project Specific Discloser Forms before participating in the Study.

17 LITERATURE REFERENCES

- Houston KE, Tomasi M, Yoon M, Paschalis EI. A Prototype External Magnetic Eyelid Device for Blepharoptosis. Translational Vision Science & Technology. 2014; 3(6):9.
- Houston KE, Tomasi M, Yoon M, Batalha G, Paschalis EI. An external magnetic device for **severe bilateral blepharoptosis**: proof of concept (abstract). Optom Vis Sci 2015; E-abstract 15092.
- Lawrence G, Paschalis EI, Tomasi M, Finch N, Houston KE. A non-invasive magnetic system for temporary management of **lagophthalmos**- proof of concept (abstract). Optom Vis Sci 2016;93: E-abstract 16091.

- Singh NK, Paschalis EI, Tomasi M, Rizzo JF, Houston KE. The boston blink-netic project: preliminary **outpatient feasibility** results (abstract). Optom Vis Sci 2016;93: E-abstract 16118.
- Houston KE, Pachalis EI, Angueira DC, Bronstad PM, Barrett AM, Iaccarino MA. Restoration of Vision After Brain Injury Using Magnet Glasses. Am J Phys Med Rehabil 2017 Apr;96(4):e70-e74.
- **Houston KE, Tomasi M, Armaral C, Finch N, Yoon MK, Paschalis EI. The Magnetic Levator Prosthesis for Temporary Management of Severe Blepharoptosis: Initial Safety and Efficacy. Transl Vis Sci Technol, 2018. 7(1): p. 7.**

APPENDIX

Version	Date	Significant Revisions