A single center sham and active controlled double blind randomized crossover trial of the magnetic levator prothesis for severe blepharoptosis

ClinicalTrials.gov title: Clinical Trial Comparing Two Non-Surgical Treatments for Severe Blepharoptosis

ClinicalTrials.gov ID number: NCT04678115

Institutional IRB title: Clinical Trial to improve the magnetic levator prosthesis (MLP) including the development and testing of a novel adjustable force system and comparison to the Kinesio Tape frontalis sling (KTFS)

Institutional IRB Protocol Identifying Number: 2019P003055

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Disclosure:

E.I. Paschalis and **K.E. Houston** are named on a US patent application assigned to Schepens Eye Research Institute for the technology that is the topic of this research. The institution has reviewed this potential conflict and the authors have followed any requirements for management. The IP is not currently licensed and the device is not commercially available. **E.I. Paschalis** is also a paid consultant for Strategic Intelligence Inc. but is not a conflict to this work.

LIST OF ABBREVIATIONS

MLP	Magnetic levator prosthesis
IPF	Interpalpebral fissure
PI	Principal Investigator
NEI	National Eye Institute
NAFL	Sodium Fluorescein
IRB	Institutional Review Board
MEEI	Massachusetts Eye and Ear Infirmary
HRPP	Human Research Protections Program
MMSE	Mini Mental Status Exam
KTFS	Kinesio Tape frontalis sling
aQoL	Assessment of Quality of Life
EQ-5D-5L	Euro Quality of Life Questionnaire
GBI-5F	Glasgow Benefit Inventory

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: A single center sham and active controlled double blind randomized crossover trial of the magnetic levator prothesis for severe blepharoptosis

Outcome measures

Primary outcome: Difference between MLP and KTFS in the change in interpalpebral fissure during and spontaneous blinking

Secondary outcome: Difference between MLP and KTFS in the changes in interpalpebral fissure during opening and volitional blinking

Secondary outcome: Proportion of subjects selecting each device at the end of the crossover

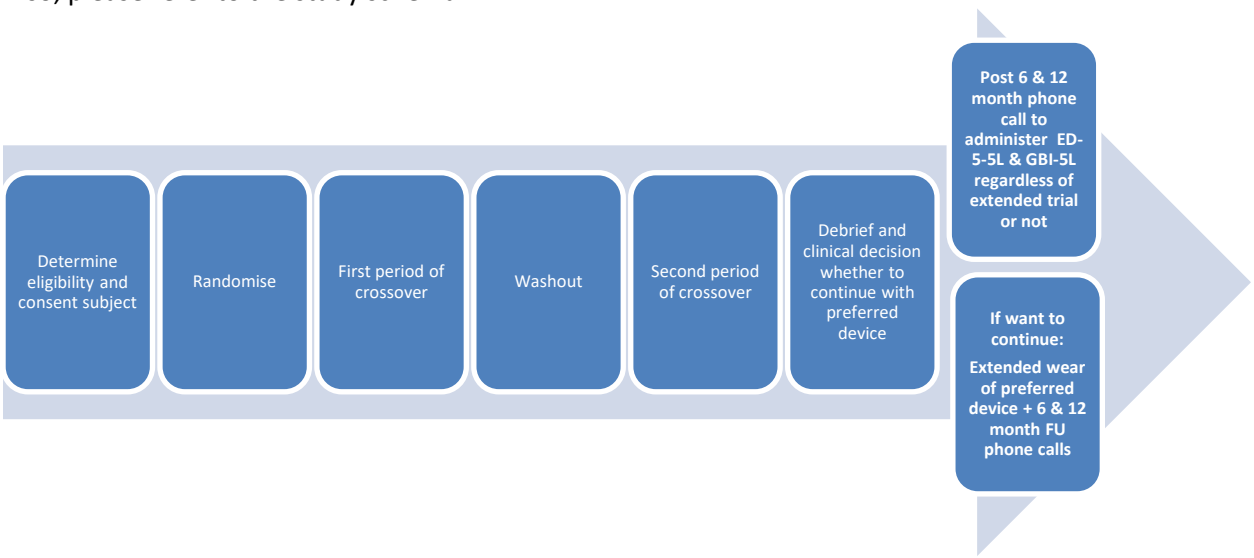
Population: Individuals with severe unilateral or bilateral ptosis defined as occlusion of the visual axis by the lid in the resting state

Phase: N/A

Number of Sites enrolling participants:	1
Description of Study Agent :	Magnetic levator prosthesis (MLP) with compatible spectacle frames Kinesio Tape frontalis sling (KTFS)
Study Duration:	2 to 3 years
Participant Duration:	8 or 9 weeks from enrollment to the end of the crossover period of the clinical trial, with an additional 8 weeks after the end of the crossover for subjects who have a clinical decision to participate in the extended wear part of the clinical trial

SCHEMATIC OF STUDY DESIGN

Also, please refer to the study schema:



FU: Follow up

1 KEY ROLES

Principal Investigator – Overall responsibility for all study related activities.
Co-investigator (clinical trial lead): Responsibility for randomized crossover clinical trial management.
Clinical Research Technicians- Responsible for consenting, enrolling and scheduling subjects. Also will collect, record and report all study data, and fit and train for the MLP device and the tape (KTFS) as a backup plan.
Physical Therapy Advisor: Training of clinical study staff and monitoring the quality of fitting for the KTFS.
Engineering research fellow: Responsible for: Assembling MLP devices and maintaining device logs
Independent safety monitor: Examine participants with adverse events and review all safety outcome reports.

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. A newly released eye drop (Upneeq, Osmotica/RVL, January 2021) has recently been approved for mild age-related ptosis (might be used off label for severe myo or neurogenic ptosis), but its effects are unknown for severe ptosis.

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, the 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. In the first part of this study the magnetic levator prosthesis (MLP) was improved by development and testing of a novel adjustable force system and in the second part of the study the MLP will be compared to another non-surgical treatment for blepharoptosis, the Kinesio Tape frontalis sling (KTFS)

2.3 Potential Risks and Benefits

2.3.1 Known Potential Risks

Risks related to use of the MLP:

Risk 1: Dryness or soreness in the eye or on the lid skin from prolonged use of the MLP has been reported in 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.

Risks related to KTFS taping:
Kinesio Tape is FDA registered with an indication for extended use on the skin. Clinically it is most often used on the upper extremities to support sore or injured muscles. It is also often used on the face for facial palsy [7], and sometimes on the eye lids for blepharoptosis. It is easily removed without any special tools or procedures. Similar to the MLP, there is the possibility that participants might experience ocular surface drying and discomfort. There is also a possibility of skin irritation from the tape. Participants, parents, and involved caregivers will be given specific instruction on how to identify problems and when to remove the tape.

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 provide a higher level of evidence for the MLP as an emerging treatment, and to determine barriers to displacing current non-surgical and temporary approaches.
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.

4 **STUDY DESIGN AND ENDPOINTS**

4.1 **Description of the Study Design**

The study is a double-blind, randomized crossover clinical trial comparing two non-surgical treatments, the MLP and KTFS, for blepharoptosis. After the end of the crossover, there will be an optional extended wear period in which participants may be invited to continue using the preferred device for up to another six months, if clinically appropriate.

4.2.1 **Primary Endpoints**
A difference between MLP and KTFS of at least 1mm in the change in interpalpebral fissure during opening and spontaneous blinking.

5 **STUDY RECRUITMENT, ENROLLMENT AND WITHDRAWAL**

Patient Gateway for recruitment will be utilized.

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. (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)

5.2 Participant Exclusion Criteria:

1. Absence of ptosis which occludes the visual axis
2. Presence of a corneal ulcer of any size, unless managed with a protective contact lens or other method and permission is granted from the candidate's managing eye doctor.
3. Age less than 5,
4. Severe Cognitive impairment defined as MMSE score <18, behaviors consistent with delirium (combinations of disorientation, hallucinations, delusions, and incoherent speech), or lethargy.
5. Presence of corneal hypoaesthesia unless cleared for enrollment by a cornea or contact lens specialist;
6. Orbicularis weakness on the side of the ptosis.
7. Mechanical ptosis, including ptosis due to orbital or lid tumor, cicatricial processes affecting the movements of the upper lid, and enophthalmos.
8. Previous ptosis surgery less than 3 months prior to Visit 1.
9. Lid position affected by lid or conjunctival scarring.
10. History of herpes keratitis.
11. Periocular neurotoxin (eg, Botox, Xeomin, Dysport, Myobloc) injections on the side of the ptosis within 3 months prior to Visit 1 and during the study.
12. History of hyperthyroidism or thyroid eye disease (ie, exophthalmos, upper eyelid retraction, diplopia secondary to extraocular muscle involvement). Hypothyroidism that is controlled on medication is allowed.

Hypoaesthesia and chronic corneal ulcers may be treated successfully, usually with artificial tears and/or a protective contact lens. Therefore, when there is hypoaesthesia or chronic epithelial defect the PI will contact the candidate's cornea or contact lens specialist (e.g. via email or EMR message (EPIC)), and request permission to enroll the candidate. If they do not have a cornea or contact lens specialist, a consult with one at MEE who is not affiliated with the study will be requested prior to enrollment.

5.3 **Strategies for Recruitment and Retention**

Subjects will be recruited from two main sources:

1. Subjects will be recruited from the PI's clinical practice, which specializes in patients with low vision related to neurological conditions. Several ophthalmologists, neurologists, and physiatrists in the MGB system are aware of the PI's expertise in severe neuro and myogenic ptosis and associated strabismus, and routinely refer their patients to the PI's clinic where they will be offered participation if appropriate. Subjects recruited from the PI's clinic will be contacted by telephone, email or letter with brief details about the study (see attached telephone script and email/letter script). For participants who are among the investigator's own patients, the risks of coercion or undue influence will be minimized by having a study team member other than the PI contact the patient about the study.

2. Subjects will be recruited from other relevant clinics within the MGB network (e.g., the MGH neuromuscular clinic). Non-study staff physicians at MEEI and other local Boston

area practices within the MGB network will be sent a letter (see uploaded practitioner's letter) asking them to provide approved study recruitment flyer (see uploaded flyer) to potential participants. The flyer includes contact information so the participant can directly contact a member of the study team. In addition, flyers may also be posted in public areas in clinics, when permitted.

We do not anticipate any problems with subject retention. Typically patients are eager to participate because we are providing treatments that may improve eye opening. Subjects will receive regular follow ups which will help facilitate retention. Participants will receive remuneration for participating in this research study. They will receive $60 at the end of the second period of the crossover (typically visit 6). This will be done using a Clini~~-~~Card.

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:

1. Investigator determination that it is not in the best interest of the subject to continue participation
2. Serious adverse events
3. 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**

Magnetic Levator Prosthesis (MLP):
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.

Kinesio Tape Frontalis Sling (KTFS):
Kinesio Tape is FDA registered as a 510K exempt class 1 device, typically used by physical and occupational therapists to support muscular healing and movement. It is sometimes used on the face in cases of facial palsy or on the eye lid to support the lid in cases of severe blepharoptosis. In such cases it may be attached near the lid margin above the lashes extending up to the forehead skin overlying the frontalis muscle. Alternatively it may be a very short piece attached only along the lid skin. The tape is easily removed.

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. Kinesiotape will be acquired from Kinesio Holding Corporation, Albuquerque, NM.

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

6.1.10 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 be 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.

Kinesio Tape is FDA registered as a 510K exempt class 1 device, typically used by physical and occupational therapists to support muscular healing and movement. It is currently used as a treatment to support the lid in cases of severe blepharoptosis. As such an IDE should not be required.

6.2 Study agent Accountability Procedures

The devices will be stored in the lab offices at Schepens Eye Institute and dispensed at Massachusetts Eye and Ear in the vision rehabilitation service clinical research lab (8th floor, 243 Charles St). Logs will be kept by the Research Assistant and Engineering Research Fellow to keep account of which devices were 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

The following procedures will be performed as part of the study (see schedule of events table in section 7.3.7.)

1. Refraction (if needed)
2. Visual acuity
3. Slit lamp examination of external eye, lid and cornea with Nafl & NEI scale
4. Comfort rating
5. Video recording of eye blinks
6. Rating of skin integrity
7. EQ-5D-5L questionnaire
8. GBI questionnaire
9. aQoL questionnaire

Based on experience, we anticipate that the first study visit will typically last about 120 minutes and subsequent visits about 60 minutes.
Some of the visits will be conducted virtually (as detailed in subsequent sections). To facilitate virtual visits, a visual acuity chart will be given to the subject to allow this safety outcome monitoring remotely and other safety outcomes will be conducted during the call (comfort scale, inspection of the external eye and lid skin).

Detailed plan for REDCap text message and email communication:

A short three-question survey will be used to document whether subjects are wearing a device during the periods of home use. Consent to receive a survey link by text message or email will be documented in the consent form along with the preferred contact method (text, email, or both). For subjects that consent to receive the survey links, their preferred phone number and/or email address will be recorded on a sheet separate from the consent form, which will be kept in a locked cabinet in a locked office. As soon as the phone number and/or email address have been input into REDCap, the original will be shredded.

Subjects who consent to receive the survey links will receive a text message or email (based on their communication preference) with a link to a REDCap survey twice daily when using one of the devices at home during the trial week. Please see uploaded document for details of the survey language and questions. Subjects will be able to decline receiving the survey links at any time.

Text message plan: Text messages will be sent to subjects using the Twilio platform. The "Survey as webpage" option will be selected so that subjects can access the REDCap survey URL directly from the text. Subjects' phone numbers will only be entered if they consented to receiving messages in this way. A sentence in the text message will notify the subject that they can opt out of receiving these texts by replying "Stop".

Email plan: In the event that subjects prefer to be contacted by email, they will receive the link to survey sent to their email through the REDCap platform. The "automated invitations" option will be used to send out emails at certain times of day to the subjects. Subjects' emails will only be entered if they consented to receiving messages in this way. A sentence in the email message will notify the subject that they can opt out of receiving these emails by replying "Stop".

7.3 **Study Schedule**

The study schedule is summarized below (section 7.3.7).

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 to return with a caregiver (if one is not present). If score is <18, they will not be eligible.

Screening: Subjects with MMSE scores of at least 18 will undergo consent procedures at the start of the first visit. After consent, the eligibility check list (uploaded) will be used to determine eligibility. Only eligible subjects will be enrolled in the clinical trial.

7.3.2 **CROSSOVER**

After consent and enrollment, subjects will be randomly assigned to one of the two arms for the crossover period. In one arm subjects will receive the MLP first and the KTFS second. In the other arm, subjects will receive the KTFS first and the MLP second.

Each period of the crossover will last for about three weeks, including about two weeks of training in how to apply and remove the device followed by about one week of using the device at home. Training will be conducted at study visits at Mass Eye and Ear. Typically there will be two training visits. Baseline measures of eye lid blinking without and with the device will be taken during training. For the MLP, two baseline measures of eye lid blinking will be recorded one with the real MLP device and one with a sham MLP device to determine how much improvement might occur simply through a placebo effect. However, for the KTFS it will not be possible to take a baseline measure with a sham KTFS. Only subjects and caregivers who demonstrate sufficient ability to apply and remove the device will be permitted to take it home. During the period of home wear, there will be a video call every other day to monitor the subject's use of the device and safety. During the kfts arm, an occupational or physical therapist consulting with the Massachusetts eye and ear study team may talk with the subject during the video conference call to ensure that the kinesio tape is in the correct position. Mass General Brigham approved software will be used for video calls. During the trial week of home use of devices, subjects will

also receive REDCap survey link notifications each day to complete a brief survey to log if they are wearing the device (see the detailed plan above, and see attached document for survey language and questions).

To ensure no carry-over effects, there will be a washout of about 2 weeks duration between the first and second period of the crossover during which subjects will not be permitted to use any device for their blepharoptosis. (This will be similar to their habitual state before enrollment since none of the participants would have been using any device for their blepharoptosis about two weeks before enrollment).

At the end of the second period of the crossover, subjects will receive a phone call at which the comparison questionnaire (comparing the two devices) and the debriefing questionnaire will be administered. Subjects who express a preference for one of the devices and are interested in continuing to use the preferred device will be asked to attend Mass Eye and Ear for a study visit with Dr. Merabet determine whether it is clinically appropriate for them to continue with the preferred device. Subjects who do not wish to continue with either of the devices will have no further in-person study visits after this point (but will be asked to complete the 6 and 12 month telephone follow ups), and they will be asked to return the study device unless they get special approval from the clinic to keep it as part of their continued treatment.

7.3.3 **EXTENDED WEAR Follow-up**

Only subjects for whom the study doctor determined it was clinically appropriate to continue with the preferred device (either MLP or KTFS) will be invited to participate in the extended wear part of the clinical trial. The extended wear will involve about six months of home-use of the preferred device with a study visit at every one month period. More frequent monitoring visits may be requested by the study doctor based on clinical judgment. During the extended wear period, subjects may also receive REDCap survey link notifications each day to complete a brief survey to log if they are wearing the device. Please see section 7.3.7 for procedures that will be conducted at follow up visits.

7.3.4 **Final Study Visit**

At the final study visit (at the end of the extended wear) a clinical decision will be made as to whether or not the MLP or KTFS is recommended for continued use. Participants will be allowed to take the preferred device (MLP or KTFS) and continue wearing it, if considered clinically appropriate, and transferred to the clinical practice of the PI.

7.3.5 **Long-term follow up: 6 and 12-month telephone follow ups**

All subjects will be called at 6 & 12 months after the final study visit to complete some of the same questionnaires from earlier in the study (regardless of participation in extended trial). If subjects had continued using the device after the final study visit, the study staff will also ask them about device use & abandonment.

7.3.6 **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**

*Visits 8-10 are in office, approximately every second week. There will be video call follow ups on weeks without an in-office visit

		Consent	EQ-5D-5L Questionnaire	aQoL Questionnaire	GBI Questionnaire	Visual Acuity	SlitLamp, skin rating, & NEI grading	Video Recordings & Comfort ratings	Application & Removal training	Debrief and device comparison questionnaire	Clinical decision
Device 1	**Visit 1**	x	x	x		x	x	x	x		
	Visit 2					x	x	x	x		
	About 1 week wearing at home with video calls for safety monitoring and daily survey about wear time										
	Visit 3		x	x	x	x	x	x			
Washout (about 2 weeks)											
Device 2	**Visit 4**		x	x		x	x	x	x		
	Visit 5					x	x	x	x		
	About 1 week wearing at home with video calls for safety monitoring and daily survey about wear time										
	Visit 6		x	x	x	x	x	x			
End of crossover period											
	Phone call									x	
	Visit 7					x	x	x			x
Start of extended wear trial (about 6 months)											
Chosen device	**Visit 8**		x	x	x	x	x	x			
Long term follow up											
	6 month phonecall		x	x	x						
	12 month phonecall		x	x	x						

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**

If considered clinically appropriate, participants will be allowed to take the MLP and continue wearing it after completion of the study, or to continue with the KTFS after completion of the study. MEEI has already approved provision of the MLP to non-research subject patients under the Humanitarian Devices rules, and Kinesio Tape is commonly used as a treatment for ptosis.

7.10 **Virtual Visits**

REDCap consent module will be used to obtain econsent.

In 2022, the NIH provided a supplement to allow virtual enrollment of up to 10 participants to help meet enrollment goals while promoting greater diversity of the study sample. Study procedures will be identical to those described in section 7.3, but will be conducted virtually via video visit. Methods for virtual monitoring of active participants during the pandemic related shutdown were developed and successfully implemented during the in 2020, as described in prior sections. The key differences and logistical solutions needed for entirely remote participation are summarized here:

Prior to consideration for enrollment, candidates will be required to provide a copy of a complete eye exam by any licensed provider conducted within the 3 months prior to the pre-screening consent video visit. The first video visit will be for the pre-screening MMSE. A visual acuity paper chart, and supplies for corneal sensitivity testing will be mailed to candidates ahead of this first visit. Study activities will not begin until the second video visit, to allow time for participants to receive a study equipment package in the mail from us. The package will include device supplies, device application instructions, Burton lamp artificial tears and NaFl strips (for remote cornea exam), paper questionnaires, and instructions for downloading a visual acuity and external eye photography app. Everything described in section 7.3 will be done on the video visit platform including but not limited to training to self-apply the lid devices and video recording of blinking.

8 **ASSESSMENT OF SAFETY**

8.1 Specification of Safety Parameters

The safety of the study devices 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:

10. **Systemic safety**: Incidence and severity of systemic adverse events during the study (adverse events spontaneously reported or observed by the Research Assistant).
11. **Ocular safety**: Incidence and severity of ocular adverse events during the study (ophthalmic examination, adverse events spontaneously reported).

SAFETY CUTOFFS: Serious adverse events which would result in study suspension: 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 will be sent to the IRB. Corneal rating changes >1.5 points will be reviewed by the independent safety monitor at the Eye and Ear to determine if criteria for study suspension or dismissal are met, and when it may be possible to continue. Serious adverse events which will result in immediate dismissal from the study (and treatment) include: 1) development of a related corneal ulcer (as judged clinically by the independent safety monitor) with or without infiltrate or 2) broken skin on the eyelid (skin decompensation).

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:

1. Results in death
2. Is life threatening
3. Requires hospitalization/prolongation of hospitalization
4. Results in congenital anomaly
5. Results in persistent or significant disability/incapacity
6. 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:

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

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 plans are summarized in the subsequent sections.

10.2 Statistical Hypotheses

Primary outcome measure:

Statistics for the participant characteristics will be presented in terms of mean ± standard deviation or median ± interquartile range (25^{th} to 75^{th}). Within subjects repeated measurements, linear mixed effects regression will be used to determine the effect of treatment condition on the IPF values (spontaneous and resting state open), with a random intercept for the subject factor. Subject age, gender, blink sequence (the order of the blink recorded in the video), and the order of interventions (whether evaluated in the first or the second arm of the crossover) will be covariates of interest. Effect of each covariate will be investigated alone, and only statistically significant (P<.05) covariates will be included in the final regression model, from which, the estimated marginal means and their 95% confidence interval (CIs) will be reported for each of the outcomes. Missing values at the T2 time point will be imputed from another time point within the same subject (T1 by default or T0 if both T1 and T2 were not available). For volitional blinks, a test of proportionality will be performed to determine the effect of the 3 treatments on the probability of eye not fully closing.

10.3 Analysis Datasets

The dataset for the analysis of the primary outcome measure will be an intention-to-treat dataset.

10.4 Description of Statistical Methods

10.4.1 General Approach

This clinical trial uses a prospective, double-masked, within-subjects crossover design. Descriptive statistics for continuous data for each of the primary and secondary endpoints will be presented as means with standard deviations or medians and ranges, as appropriate. The normality of the data will be examined and appropriate statistics and descriptives used based on the results.

Measurements of Eye Lid Kinematics:

Our main measures of device efficacy involves the measurement of eyelid kinematics from video recordings made at various timepoints throughout the clinical trial. **Measurements may be made manually within NIH's image J software, automatically using a software we create (in Python or similar platform), or using crowdsourcing with Amazon Mechanical Turk.**

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

We will use a repeated measures mixed effects model for analysis of the primary outcome measure (change in interpalpebral fissure during opening and spontaneous blinking). The model will include a random subject-level intercept and a fixed treatment effect (MLP or KTFS). A repeated measures model will be used with primary timepoint for analysis being after 1 week of use. . The model will also include fixed effects of treatment order (i.e., MLP: KTFS vs KTFS:MLP), and crossover period (period 1 or 2), and will control for age and sham opening interpalpebral fissure.

10.4.3 Analysis of the Secondary Endpoint(s)

The change in interpalpebral fissure during volitional blinking will be analyzed using the same approach as for the primary outcome measure.Questionnaire responses will be summarized using descriptive statistics and analyzed using non-parametric tests.

10.4.4 Safety Analyses

Clinical study staff will acquire high resolution magnified images of the ocular surface and eyelid skin which will be reviewed by the PI and at least 1 other study team member with clinical training will produce quarterly reports to be reviewed by the independent safety monitor. 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, other study personnel and the independent safety monitor.

10.4.6 **Baseline Descriptive Statistics**

Baseline data will be summarized using descriptive statistics, as appropriate.

10.4.7 **Planned Interim Analyses**

10.4.7.1 **Safety Review**

The data 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. Data summaries will be sent to the independent safety monitor on a quarterly basis for a safety review (at the monitor's discretion) and to 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. There is no plan for multiple comparisons.

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**

Sample size was estimated based on available preliminary data at the time of study planning, estimating 40 would need to complete the crossover with an estimated attrition of 10 giving a total of 50 planned for enrollment. However, this was able to be greatly reduced given the size of the effects measured in the interim analyses conducted after 8 participants had completed the crossover. The final sample size required to measure the primary outcome with power of 0.80 and type II error of alpha 0.05 was 16.

10.6 **Measures to Minimize Bias**

10.6.1 **Masking AND RANDOMIZATION Procedures**

Masking:

Subjects will be masked as to which of the two devices is the new treatment. They will simply be told that they are evaluating two non-surgical treatments for blepharoptosis. A debriefing questionnaire will be administered after the second period of the crossover to determine whether subjects guessed that the MLP was the new treatment and the KTFS was the comparison treatment.

Data assessors (e.g. Turkers) for the primary outcome will be masked since they will not be familiar with the study or the 2 treatments. They will review videos of blink dynamics which have been cropped to show only the eye region so the subject cannot be identified (see Measurements of Eye Lid Kinematics in section 10.4.1).

The person conducting statistical analyses of the primary outcome will be masked.

It is not possible to mask the study team member who will fit and provide training for the MLP device, since the fitting requires specialist expertise. That study team member will avoid telling subjects that the MLP is the new treatment. Furthermore the quantification and analysis of the primary outcome will be conducted by masked data assessors.

A person external to the study team will fit and provide training for the KTFS. Again, it will not be possible to mask this person. However, this person is highly experienced in using Kinesio Tape, a proponent for its use for blepharoptosis, and has received training in fitting Kinesio Tape for ptosis. Again they will avoid telling subjects that the KTFS is the comparison treatment, and the quantification and analysis of the primary outcome will be conducted by masked data assessors.

Recruitment for the clinical trial has been very successful so far. However the greater number of subjects than initially anticipated means that we have been running into problems when trying to schedule visits with the Physical Therapy Team Member (PT) for fitting of the kinesiotape frontalis sling (KTFS). The PT sometimes does not have sufficient room in her clinic schedule to accommodate a taping visit per the schedule in the protocol. We've described a backup plan below to ensure that participants receive taping visits per the original protocol schedule even when the PT is not available. Please note that the proposed plan requires that the PT will provide oversight of all taping visits by reviewing videos of the taping sessions.

As a backup plan in case scheduling constraints mean that it is not possible to schedule a taping visit with the PT:

1. The PI will perform the tape placement.
2. The PI or the research staff will be in attendance as the participants practice placing the tape.
3. The entire process will be recorded and the video loaded onto a secure server or shared via Institutional DropBox
4. The PT will be responsible for reviewing the videos within two days of placement, to ensure proper technique.

Randomization

Participants will be assigned to one of two possible treatment allocations: 1) MLP then KTFS or 2) KTFS then MLP. The allocation will be performed using software that implements the process of minimization. The first participant will be assigned randomly with each subsequent participant assigned in such a way as to approximately balance the number of participants who are 65 years of age and over and who have acute vs chronic ptosis. We propose to balance for these two factors because adults over the age of 65 typically have thinner and looser eyelid skin, and participants with acute ptosis may recover while enrolled in the study, which may affect outcomes. Letter codes, randomly assigned to each of the treatment allocations by a researcher external to the study will be used by the software. The code breaker will be kept in a sealed envelope in a location known only to the external researcher. Data provided to the masked data assessors and the masked person conducting statistical analyses will use the letter codes to identify treatment allocation.

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 research technician (oversight by PI) will review and sign each subject visit for completeness and document any minor protocol deviations. 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 Principal 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 Mass General Brigham IRB. The protocol will be approved prior to subject enrollment and will be reviewed yearly after initial approval. Any adverse events or serious adverse events will be reported to the Mass General Brigham IRB 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 team 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 Mass General Brigham 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

Consent and assent forms have been uploaded.

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 Vision Rehab Service research lab at Massachusetts Eye and Ear Infirmary, 243 Charles St., 8th floor. 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 and assent for decisionally impaired: 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 (may be decisionally impaired), 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)).

Children: 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).

Consent procedures: The PI has approximately 10 years experience in providing informed consent to patients with neurological disorders, and >15 years providing eye care for this population. One of the trained clinical research technicians will perform the informed consent in a private room at Massachusetts Eye and Ear. The PI will not be directly involved in the consent process and he will not be in the room during signature, to prevent any sense of pressure/coercion. Alternatively, informed consent may be performed over the telephone, to limit the face to face time so long as the COVID-19 pandemic is a concern. 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 devices (pictures of the devices if consented on the phone) and allowing them to ask questions. The study staff 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 the PI, 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 MGB IRB. Paper data forms will be stored in a locked file cabinet in the vision rehab lab on the 8th floor at Mass Eye and Ear 243 Charles St. Boston MA 02114, or 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 following the MGB IRB 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 MGB Human Protection Program policy, the Principal Investigator and Sub Investigators will complete the MGB IRB Conflict of Interest In Research Project Specific Disclosure Forms before participating in the Study.

17 LITERATURE REFERENCES

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