Efficacy of Intermittent Occlusion Therapy Glasses for Amblyopia

NCT02687581

ID: HJW1602

- **Protocol: 12/18/2018**
- **Informed consent forms:**
    - **Randomized trial consent form A for dense amblyopia: 12/18/18**
    - **Observational trial consent form B for deprivation amblyopia: 02/08/16**
    - **Observational trial consent form C for myopic anisometropic amblyopia: 09/19/16**
- **Statistical analysis**

PROTOCOL SUMMARY

INSTRUCTIONS: In order to review your proposal, the IRB must have the following information pursuant to its charge by HHS Regulations 45 CFR 46 and FDA Regulations 21 CFR 50.56. Each subpart must be titled using **boldface subheadings** as described below and addressed independently in the listed sequence without reliance on information covered under other subparts. Attachment of applicable sections of the grant application is not acceptable as a substitute for completion of each subpart. Please include sufficient information to facilitate an effective review by all members of the IRB including non-specialists. All abbreviations and terms not part of common medical usage should be defined and simplified language should be used as much as possible. Unless justification is provided, this part of the IRB application has an absolute limit of ten (10) pages excluding references. These pages should be numbered.

PURPOSE OF THE STUDY AND THE BACKGROUND (1-2)

1. **Purpose of the Study**.

This study is designed to evaluate the effectiveness of a novel amblyopia treatment – Intermittent occlusion therapy (IO-therapy) glasses (Amblyz™) in treating amblyopia: severe, deprivation and myopic anisometropic amblyopia.

Children ages 3 to < 8 years with **severe/dense** amblyopia (visual acuity of 20/100 to 20/400 in the amblyopic eye) will be enrolled and randomized into two groups: 1) standard 6-hour patching group or 2) 12-hour IO-therapy glasses group.

Children ages 3 to < 8 years with **deprivation** amblyopia associated with congenital or developmental cataracts (visual acuity of 20/40 to 20/400 in the amblyopic eye) will be enrolled. According to visual acuity, they will receive one of two IO-therapy glasses treatment regimens: 1) If the amblyopic eye is between 20/40 to 20/80 inclusive, 4-hour IO-therapy glasses or 2) If the amblyopic eye is between 20/100 to 20/400 inclusive, the child will receive12-hour IO-therapy glasses.

Children ages 3 to < 8 years with **myopic anisometropic amblyopia** will be enrolled into an intermittent occlusion therapy glasses (Amblyz™) group.

2. **Background**.

Amblyopia is the most common cause of monocular visual impairment in children. The major cause of amblyopia is due to the fact that unbalanced visual experience at an early age induces the mal-development of the neural system. The primary goal of amblyopia treatment is to restore normal visual function both in the visual acuity of the amblyopic (weak) eye and in the binocular cooperation between the eyes.

Current and accepted treatments attempt to enforce the utilization of the amblyopic (weak) eye by obstructing or blurring the vision of the sound eye using eye patching or penalization drops. In these ways, visual experience of the amblyopic eye is enhanced. The mal-development of the neural system can be reversed, at least to some extent, during the plastic period (from birth to 10 years of age) of the visual cortex.

Although these existing treatments are effective, many children fail to achieve normal visual acuity in the amblyopic eye. .[1,2] Thus, effective treatment for amblyopia, particularly severe amblyopia is in an urgent need.

Electronic eyeglasses, IO-therapy glasses (Amblyz™), are a new medical device designed to treat amblyopia. They are based on intermittent shuttering of one of the lenses, which are made of high-tech liquid crystal material. IO-therapy glasses are formed in shape of glasses to facilitate its use and worn the same way as normal optical glasses. The technology was tested in clinical settings and was proven to be safe and efficient.[3, 4]

Benefits of IO-therapy Glasses

1. Periodical occlusion is more convenient to the child in his daily activities thus increases compliance.

2. Periodical occlusion enforces binocular vision exercise.
3. Technology allows patient/child to enjoy an active, normal lifestyle.
4. No allergy issues as with an eye-patch.

A non-randomized study reported that IO-therapy glasses yield an improvement in the amblyopic eye and offer an effective, alternative treatment.[4] However, there is no randomized clinical trial to further investigate IO-therapy glasses as a treatment of amblyopia.

According to our pilot study, IO-therapy glasses work well with **moderate** amblyopia. However, 25% of amblyopes are **severe** amblyopia. To treat amblyopia, previous studies showed that 6-hours of patching is effective. Therefore, if we treat **severe** amblyopia with IO-therapy glasses, we need 12-hours of wearing of IO-therapy glasses.

Most children with deprivation amblyopia who had unsuccessful patching treatment need an alternative treatment. According to our pilot study on moderate amblyopia, we postulate that intermittent occlusion might be effective for deprivation amblyopia.

In addition, children with myopic anisometropic amblyopia are often difficult to treat with patching. We postulate that intermittent occlusion might be effective for myopic anisometropic amblyopia.

CHARACTERISTICS OF THE SUBJECT POPULATION (3-10)

3. **Target Accrual**. What is the number of subjects to be enrolled at Salus University and the number at any external study site(s)? What is the total number of subjects in the case of multicenter protocols? *Note: the number of subjects to be enrolled in the study should be based upon medical, scientific, and statistical considerations*.

With a computer program with block design, twenty-eight patients will be randomized in each of the two treatment groups, for a total of 56 patients with **severe** amblyopia.

We plan to enroll patients at the following sites:
1) Indiana University
2) Illinois College of Optometry
3) Conestoga Eye Clinic site (Lancaster, PA)
4) Nemours Alfred I. duPont Hospital of Children (Wilmington, DE)
5) Arkansas Children's Hospital (Jones Eye Institute, Little Rock, Arkansas) (new site)
6) St Christopher's Hospital for Children, Phillidalphia, PA. (new site)

Each site will work on the enrollment until we reach the total goal N=56 patients with **severe** amblyopia, 15 patients with **deprivation** amblyopia, and 10 patients with **myopic anisometropic** amblyopia. Enrollment will cease when the total is goal reached.

The total number of children is 81.

The number of patients per site, as included herein, is our goal and are, therefore estimates. If a site enrolls more patients than expected, the numbers to be enrolled at the alternate sites will be adjusted so that the final number of patients for each condition is not changed.

For the **severe** amblyopia study:
This is a pilot study on severe amblyopia. We adopt the same sample size as the calculation for moderate amblyopia, which is 28 for each group and a total of 56 patients.

4. **Gender of the Subjects**.

Male and female subjects are equally eligible to participate in this study.

5. **Age Range of Adult Subjects**.

6. **Age Range of Pediatric Subjects**. What is the age range of subjects who are children? What is the rationale for selecting this age range? If children are excluded, justification should be provided. *Note: Children should not be excluded from participating in clinical research unless there are justifiable scientific, ethical, or other reasons not to include them*.

The age range of pediatric subjects in this study is 3 to <8 years of age. Rationale for selecting age is to be consistent with the PEDIG Amblyopia studies. This age range is the most effective age for occlusion treatment.

7. **Racial and Ethnic Origin**.

There are no participant restrictions based on race or ethnic origin.

8. **Inclusion Criteria**. What are the specific inclusion criteria?

If patients are in the severe amblyopia category, the following criteria must be met for the patient to be enrolled in the study:

1. Age 3 to < 8 years
2. Amblyopia associated with strabismus (commitant or incommitant), anisometropia, or both

- Criteria for strabismus: At least one of the following criteria must be met:
    - Heterotropia at distance and/or near fixation on examination (with or without spectacles)
    - History of strabismus surgery
    - Documented history of strabismus which is no longer present (which in the judgment of the investigator could have caused amblyopia)
- Criteria for anisometropia: At least one of the following criteria must be met:
    - >0.50 D difference between eyes in spherical equivalent
    - >1.50 D difference between eyes in astigmatism in any meridian

3. Visual acuity, measured in each eye without cycloplegia within 7 days prior to enrollment using the ATS single-surround HOTV letter protocol as follows:
    - Visual acuity in the amblyopic eye between 20/100 and 20/400 inclusive
    - Visual acuity in the sound eye 20/32 or better
4. Spectacle correction (if applicable) for measurement of enrollment visual acuity must meet the following criteria and be based on a cycloplegic refraction within 6 months:

- Requirements for spectacle correction:
    - For patients meeting criteria for only strabismus (see 2.2 #2 above)
        i. Hypermetropia if corrected must not be undercorrected by more than +1.50 D spherical equivalent, and the reduction in plus sphere must be symmetric in the two eyes. Otherwise, spectacle correction is at investigator discretion.
    - For patients meeting criteria for anisometropia or combined-mechanism (see 2.2 #2 above)
        i. Spherical equivalent must be within 0.50 D of fully correcting the anisometropia
        ii. Hypermetropia must not be undercorrected by more than +1.50 D spherical equivalent, and reduction in plus must be symmetric in the two eyes
        iii. Cylinder power in both eyes must be within 0.50 D of fully correcting the astigmatism
        iv. Cylinder axis in the spectacle lenses in both eyes must be within 6 degrees of the axis of the cycloplegic refraction

5. Wearing optimal spectacle correction for a minimum of 4 weeks at the time of enrollment.
6. Gestational age > 34 weeks and birth weight > 1500 grams
7. Parent willing to accept randomization
8. Parent willing to be contacted and has access to phone
9. Parent does not anticipate relocation outside area of active study site

If patients are in the deprivation amblyopia category, the following criteria must be met for the patient to be enrolled in the study:

a) Age 3 to < 8 years
b) Amblyopia due to previous congenital or developmental cataract surgery.
c) Visual acuity, measured in each eye without cycloplegia within 7 days prior to enrollment using the ATS single-surround HOTV letter protocol as follows:
    a. Visual acuity in the amblyopic eye between 20/40 and 20/400 inclusive
    b. Visual acuity in the sound eye 20/32 or better
    c. Inter-eye acuity difference ≥ 2 logMAR lines (i.e., amblyopic eye acuity at least 3 lines worse than sound eye acuity)
d) Gestational age > 34 weeks and birth weight > 1500 grams
e) Parent willing to be contacted and has access to phone.

If patients are enrolled in the myopic anisometropia amblyopia category, the following criteria must be met for the patients to be enrolled in the study.

- Aged 3 to <8 years
- Best-corrected VA in the amblyopic eye of 20/40 to 20/400 inclusive
- Best-corrected VA in the fellow eye of 20/40 or better
- Magnitude of myopic anisometropia of ≥ 3.00 D
- Intereye acuity difference of ≥ 3 logMAR lines
- Amblyopia associated with myopic anisometropia
- Has been wearing optimal spectacle correction for a minimum of four weeks

9. **Exclusion Criteria**. What are the specific exclusion criteria?

Exclusion Criteria for severe amblyopia:

- Amblyopic eye has myopia worse than -3.00D spherical equivalent.
- Previous amblyopia treatment within 6 months.
- Prior intraocular or refractive surgery
- Known skin reactions to patch or bandage adhesives
- Systemic diseases that may cause reduced vision such as Down syndrome.

Exclusion Criteria for deprivation amblyopia:

- Systemic diseases that may cause reduced vision, such as Down syndrome.

Exclusion Criteria for myopic anisometropic amblyopia:

- Presence of ocular pathology causing reduced VA
- Prior ocular surgery
- Current vision therapy

10. **Vulnerable Subjects**.

Children will be included in the study because amblyopia is an eye disease that occurs in children and there is a restricted time period for plasticity of the brain for treatment.

METHODS AND PROCEDURES (11-13)

11. **Methods and Procedures Applied to Human Subjects**.

Historical Information

Historical information elicited will include the following: date of birth, gender, ethnicity, prior amblyopia therapy (e.g., glasses, patching, pharmacologic, Bangerter filters), current spectacle correction, history of eye surgery, and allergy to adhesive skin patches.

Contact information, which includes phone numbers and addresses, will be collected.

Clinical Testing before randomization

Examination procedures include:

1. **Visual Acuity** within 7 days of enrollment

Measurement of visual acuity in each eye (weaker eye first) by the ATS single-surround HOTV testing protocol throughout the whole study. Aspects of the testing protocol that are specific to this study are:

- Visual acuity of the amblyopic eye must be tested without cycloplegia.
- Patients currently wearing spectacles must have enrollment acuity measured while wearing spectacles - trial frames or phoropter cannot be used.

2. **Ocular motility examination** within 7 days

Measurement of alignment by Simultaneous Prism and Cover Test (SPCT) in primary position at distance and near

3. **Ocular Examination** within 6 months

Complete ocular examination, including dilated fundus examination, to rule out a cause for reduced visual acuity other than amblyopia.

4. **Titmus fly and Randot Preschool Stereoacuity test** within 7 days
5. **Cycloplegic Refraction** within 6 months

Cycloplegic refraction using cyclopentolate 1%

Randomization

Randomization will use a computer-generated number with block design. Each patient with **severe** amblyopia will be randomly assigned to one of two groups:

- IO-therapy glasses treatment group: 12-hour daily IO-therapy glasses (total occlusion time: 6 hours)
- Standard patching control group: 6-hour daily patching (total occlusion time: 6 hours)

Each patient with **deprivation** amblyopia will receive IO-therapy glasses.

According to visual acuity, they will receive one of two IO-therapy glasses treatment regimen: 1) If the amblyopic eye is between 20/40 to 20/80 inclusive, 4-hour IO-therapy glasses, or 2) If the amblyopic eye is between 20/100 to 20/400 inclusive, the child will receive12-hour IO-therapy glasses.

All patients in the myopic anisometropic amblyopia group will be enrolled in the Amblyz™ group. The treatment regimen will be dependent on the visual acuity of the amblyopic eye and the eye doctor's recommendation for treatment hours. The eye doctor will follow the NIH PEDIG study suggestions: 4 hours/day of wear for moderate amblyopia and 12 hours/day wear for severe amblyopia).

For the IO-therapy glasses treatment group, the glasses will have a TheraMon® microsensor attached.[5]

For both the IO-therapy group and the patching control group:

- Treatment is continued until there is no further improvement in amblyopic eye acuity (improvement defined as >1 line) between two consecutive 12-week visits, confirmed by a re-test. Once there is no improvement of one or more lines, the patient's participation in the study is over and treatment is at investigator's discretion.

<u>Notes</u>

1. The study will provide patches or IO-therapy glasses.
2. If a patient is noncompliant with treatment, the parents should be encouraged to persist with their efforts to treat to the best of their ability.
3. Prior to deviating from the treatment protocols or prescribing non-protocol treatment, the situation should be discussed with the PI.

Randomization of Eligible Patients

1. Once a patient is randomized, the patient will be included in the analysis regardless of whether the assigned treatment is received or not. That is to adhere to "intent-to-treat" design. Thus, the investigator must not randomize a patient until he/she is convinced that the parent/guardian will accept and comply with either of the treatment regimens. Regardless of whether the patient receives the assigned treatment or not, the patient is still considered enrolled in the study and every effort should be made to perform the follow-up examinations according to the study protocol.
2. A patient is officially enrolled when the randomization process is completed.

Delay in Randomization

1. Visual acuity testing and the ocular motility examination must be performed no more than 7 days prior to randomization. If randomization is delayed beyond 7 days, then these tests must be repeated to confirm eligibility and establish the baseline measures for the study.
2. No other parts of the examination (including the refraction) need to be repeated if they were performed within 6 months prior to randomization.

Compliance

A calendar log will be maintained by all families. These logs will be reviewed at each of the protocol visits. The investigator's assessment of compliance will be recorded on the Follow-up Examination Form.

Follow-up Interactions

After randomization, all patients (from both severe amblyopia and deprivation amblyopia groups) will have the following study visits/interactions:

Telephone Call

- Each patient will be contacted by the coordinator via telephone 4 weeks following the beginning of treatment to answer any questions and to encourage compliance with treatment.
- 12 ± 1 weeks after treatment begins : primary outcome visit

Primary Outcome Visit (occurs 12 ± 1 weeks after treatment begins)

Testing will include the following:

1. **Visual acuity**
   Measured in each eye (worse eye first) by a certified examiner using the ATS single-surround HOTV acuity protocol.
2. **Titmus fly and Randot Preschool Stereoacuity test**
3. **Ocular alignment assessed with the SPCT**
4. **Re-testing of visual acuity in the amblyopic eye (if indicated)**
   If amblyopic eye visual acuity has not improved from randomization by at least one line, then the acuity will be re-tested at this visit.

The results of the re-test will be used only to determine if the patient will continue study participation with the same study-mandated treatment. The first visual acuity will be used as the primary outcome visual acuity. If neither the test nor the re-test is one line better than the visual acuity at treatment, then study participation ends.

Follow-Up Visits after the Primary Outcome Visit

For patients in either treatment group with at least one line of improvement in amblyopic eye acuity at the primary outcome examination, follow-up visits will occur every 12 ±1 weeks until no improvement of one or more lines is seen.

At each post-primary outcome visit, visual acuity will be measured in each eye (worse eye first) by a certified examiner using the ATS single-surround HOTV acuity protocol. Acuity in the amblyopic eye will be re-tested during the visit if visual acuity has not improved from the last visit by at least one line.

Future treatment plans depend on each visual outcome in the amblyopic eye:

- If the patient's vision in the amblyopic eye is improved 1-2 lines, continue the study for another 12 weeks;
- If no improvement for one visit, continue the study for another 12 weeks;
- If no improvement for two visits, stop.

Study participation will end only after a post-primary outcome visit at which amblyopic eye acuity shows no improvement of one or more lines on both an initial test and on a confirmatory re-test.

For all follow-up visits:

- Compliance will be evaluated with calendar log and microsensor.
- For patients who wear glasses with microsensors attached, data will be logged by connecting the microsensors to the reading station via antenna at 2–3 cm distance from the antenna. A USB cable transfers the data to a PC for storage; wearing times will be evaluated using the TheraMon® Software and compared to the wearing times protocol. Data will be recorded on the Follow-up Examination Form.

Test	**Visit / Interaction**			
	Enrollment	*4 wk phone call*	*Primary Outcome 12 ± 1 wk (by masked examiner)*	*Every 12 ± 1 wks after primary outcome** (by masked examiner)*
Telephone call		X		
Distance acuity each eye*	X		X	X
Ocular alignment	X		X	X
Titmus Fly	X		X	
Randot Preschool Test	X		X	
ATS questionnaire			X	X

* Using ATS single-surround HOTV acuity testing protocol on study certified vision tester.

** For patients whose amblyopic eye acuity has improved by ≥1 line at the 12-week visit, visits occur every 12 ± 1 weeks until no improvement of one or more lines.

Additional visits can be performed at the discretion of the investigator. A Follow-up Examination Form should be completed for every exam (not just the minimum required exams).

Extension Studies after Primary Outcome

For patients who are randomized in the control patching group, after primary outcome at 12 weeks, if the patients desire to use IO-therapy glasses for treatment, they can use IO-therapy glasses for treatment as an extension study. This will not apply for those patients with deprivation amblyopia.

Stereoacuity

Differences between treatment groups in stereoacuity at the 12-week outcome will be assessed using a comparison of the distributions with the exact Wilcoxon rank sum test.

Primary Analysis for Safety

Sound Eye Acuity Data

The loss of 2 or more lines in sound eye visual acuity from baseline to the 12-week masked exam will be tabulated for each treatment group.

Ocular Alignment

Ocular alignment will be assessed at baseline and at 12 weeks after randomization. Development of new strabismus (no tropia at baseline and the presence of near and/or distance tropia at follow-up) or an increase from baseline >=10 PD will be tabulated by treatment group. Similarly, disappearance of a heterotropia and a decrease in the angle of a preexisting strabismus by >=10 PD will be tabulated.

Sample Size:

The sample size for this study was calculated based on a standard two-sided trial with a continuous outcome. The calculations assume 5% type I error with 80% power; the standard deviation of change from the baseline was 0.14, and the effective size difference was 0.12. Therefore, we anticipate that we will require 46 total subjects (i.e., 23 for each group).[4] Because the IO therapy glasses are a novel device used to treat severe amblyopia, we are uncertain how many 3-8 year-old patients will drop out from the study. According to an average 15% dropout rate in previous amblyopia studies[1, 6], we overestimate the sample size to be 28 in each group to account for attrition.

12. **Drugs and Devices**. Does this study involve investigational drugs or devices (test articles) and/or FDA approved drugs/devices used for off-label purposes? If the study involves a test article, identify the drug/device, provide the IND or IDE number and identify the holder of the number. If the study involves drugs/devices used for off-label purposes, this should be stated. If the study does not involve any test articles or drugs/devices used for off-label purposes, this should be stated. *Note: Research involving investigational drugs must comply with the FDA IND Regulations (21 CFR 312) govern research with medical devices. The FDA IDE Regulations (21 CFR 812) govern research with medical devices. In some cases it may be in the best interest of the subject and the investigator for an IND/IDE to be submitted to FDA even when there is no legal requirement*.

Yes. We use IO-therapy glasses and thermosensor. We attach the medical device form of IO-therapy glasses and thermosensor. IO-therapy glasses are FDA approved.

13. **Data Storage and Confidentiality**. Where will the research data be stored during the study and how will it be secured? Who will have access to the data? If data with subject identifiers will be released, specify the person(s) or agency to whom this information will be released. *Note: The investigator must take all necessary steps to maintain confidentiality of data. This includes coding data and choosing an appropriate and secure data storage mechanism that will prevent unauthorized access to the data*.

Patient-related documents (consent forms and measurement reports) will be locked in a safety cabinet and only approved personnel can access. The office with cabinet is locked after work. When data are analyzed to report in presentation or publication, only coded ID number and age of patients may be reported.

All study related procedures will be done in a private area, office or exam room, at a scheduled time.

RISK/BENEFIT ASSESSMENT (14-20)

14. **Potential Risks**.

Risks of Examination Procedures

The procedures in this study pose no more risk than daily pediatric eye care practice in the United States. Cyclopentolate, an eye drop, may be used to dilate the child's eyes at the enrollment exam, and may sting for a few seconds. The child's pupils may remain dilated for the rest of the day, and in some cases may remain dilated for a few days. In very small children, less than 2 years of age, very rarely one or more of the following reactions have been reported to occur: flushed skin, diarrhea, increased heart rate, and seizures.

Risks of Patching

If skin irritation occurs, the parent will be advised to put an emollient on the skin and discontinue use of the patch for a day. Patching could potentially decrease the visual acuity in the sound eye, although this is almost always reversible. However, this occurrence is extremely unlikely since the sound eye will have several hours without occlusion each day. The diagnosis and management of reverse amblyopia is left to the investigator's judgment. Patching could precipitate the development of an ocular deviation (strabismus), although this has been found to be very rare in previous studies and indistinguishable from the natural history of strabismus. If treatment precipitates the development of an ocular deviation (e.g., esotropia in child with hyperopia), the parent will be advised to have the patient see the investigator as soon as possible.

Risks of IO-therapy glasses

The children adjust to the flickering of the lens of the strong eye easily. At the beginning, IO-therapy glasses may induce a transient headache or some discomfort.

However, just like traditional patching, IO-therapy glasses could potentially decrease the visual acuity in the sound eye, although this is almost always reversible. However, this occurrence is extremely unlikely since the sound eye will have several hours without occlusion each day and the risk is the same with either the IO-therapy glasses or traditional patching. The diagnosis and management of reverse amblyopia is left to the investigator's judgment. So far, there is no significant decrease (≥ 2 lines logMAR) in the visual acuity in the sound eye reported. [4]

As with traditional patching treatment, IO-therapy glasses could precipitate the development of an ocular deviation (strabismus), although this has been found to be very rare in previous studies and indistinguishable from the natural history of strabismus. If treatment precipitates the development of an ocular deviation (e.g., esotropia in child with hyperopia), the parent will be advised to have the patient see the investigator as soon as possible.

Risks of microsensor

TheraMon® microsensor is a non-significant risk device. The thermosensor records the surrounding temperature automatically every 15 minutes and is inactivated during measurements. During shorter testing or wearing periods, the software can be modified, e.g. measurement intervals can be set to 5 minutes. It transfers the collected data using radio frequency identification technology (RFID). The antenna of the sensor is only activated if positioned no farther away than 2-3 cm from the reading station. Therefore, patients wearing the microsensors are not exposed to any kind of radiation. The device is 9 x 13 mm in size and encapsulated in polyurethane. It is waterproof and does not cause any skin irritation. It is attached to the earpiece of the IO-therapy glasses, and is in direct contact with the skin. When fixed properly, the wearer has no discomfort and the chip is hardly visible because the temperature sensor just barely is in contact with the skin. If the glasses are not worn properly (e.g. to far on the nose or in the hair that they do not shutter the optical axis), temperature measurement will differ significantly (unpublished data, submission in progress). If not fixed properly, the sensor can cause pressure on the skin thus making the wearer uncomfortable and making a control of the right position impossible. In those cases a simple readjustment of the sensor-position will both improve measurement accuracy and patient comfort.

The thermosensor is in every day orthodontic use and was well tolerated. When worn attached to the earpiece of glasses, it was not reported to cause any discomfort in a pilot study[5] and in a patient collective (submission in progress).

15. **Risk Classification**.

It is the investigators' opinion that the protocol's level of risk falls under DHHS 46, which is research not involving greater than minimal risk. Additionally, there is potential benefit in that compliance with treatment may be enhanced by the intermittent occlusion nature of the IO-therapy glasses.

16. **Protection Against Risks**. What procedure(s) will be utilized to prevent/minimize any potential risks or discomfort? Does the study have a Data Safety Monitoring Board (DSMB) that will be reviewing interim results? If yes, include a brief description of the monitoring plan as well as procedures for transmitting the DSMB's summary reports to the IRB. *Note: All potential risks and discomforts must be minimized to the greatest extent possible by using procedures such as appropriate monitoring and withdrawal of the subject upon evidence of a specific adverse event or clinical signs(s). This section should reflect that all appropriate steps will be taken to protect subjects from harm. The IRB will request submission of DSMB summary reports at regular and defined intervals in order to perform on-going review of risks and benefits of this research*.

Data safety will be monitored by IRB of Salus University.

17. **Potential Benefits to the Subject**. What is the potential therapeutic benefit(s) associated with the research? *Note: Therapeutic benefit(s) refers to health benefits the subject may obtain by participating in the research*.

The subject may or may not directly benefit from the treatment.

18. **Potential Benefits to Society**.

There is potential benefit in that compliance with treatment may be enhanced by the intermittent occlusion nature of the IO-therapy glasses. The study has potential to help doctors find an equally effective or even better amblyopia treatment for children with amblyopia.

19. **Therapeutic Alternatives**. What are the therapeutic alternatives available to the subject in the non-research context that may be of reasonable benefit to the subject? If therapeutic alternatives do not exist, this should be stated and explained. *Note: This section should include a reasonable detailed description of the therapeutic alternatives that could be used to treat the patient should they elect not to participate in the protocol*.

The therapeutic alternative available is patching, atropine penalization or Bangerter filters.

20. **Risk/Benefit Relationship**. What is the relative risk/benefit relationship of the research compared with the therapeutic alternatives? *Note: The IRB relies upon a reasonably detailed analysis of the relative risk/benefit relationship of the research versus that offered by the therapeutic alternatives that are available to the subject should they choose not to participate. The relationship of the anticipated benefits versus the potential risks of the <u>research</u> must be <u>at least</u> as favorable to the subject as that presented by alternate therapies that are considered standard treatment for the disease in question. This section should clearly document that the research offers the subject an acceptable risk/benefit relationship when compared with the therapeutic alternatives.*

Compare to benefit that we may find an effective treatment for amblyopia, risk associated with this study is minimum.

FINANCIAL OBLIGATIONS AND COMPENSATION (21-23)

21. **Financial Obligations of the Subject**.

The eye patches and optical corrections for IO-therapy glasses will be provided by the study at no cost. IO-therapy glasses will be loaned to patients. The patient or his/her insurance company will be responsible for the costs of visits that would be needed whether they were in the study or not (standard care visits). The enrollment visit, if needed, is at no charge.

22. **Research Versus Standard Treatment Costs**. Are any financial obligations of the subject incurred or increased as a result of procedures performed solely for research purposes? If so, provide additional detail. *Note: The financial obligations of the subject may be increased as a result of research participation by such factors as additional diagnostic/follow-up tests; longer hospitalization; and/or administration of drugs/agents that are more expensive than alternatives. This section should clarify the subject's financial obligations relative to their participation in the research.*

The patient or his/her insurance company will be responsible for the costs of visits that would be needed whether they were in the study or not (standard care visits). Subjects will not pay extra money.

23. **Financial Compensation for Participation**.
The parent/guardian of each patient will be compensated $25 for each follow-up visit, and $50 for the primary outcome visit. For patients remaining in follow-up after the 12-week visit, $25 will be paid for each 12-week interval visit, up to an additional $100 (4 exams). All payments will be made using ClinCard. Subject would not be paid for a 5th or 6th visit.

Testing	Visit Schedule	Time	Payment
Enrollment testing		30-60 mins	$25
Primary Outcome Visit	12 weeks after treatment begins	30-60 mins	$50
Follow-Up Visits after the Primary Outcome*	12 weeks	30-60 mins	$25
	12 weeks	30-60 mins	$25
	12 weeks	30-60 mins	$25
	Continue visits every 12 weeks until no improvement	30-60 mins	N/A
Total			

*follow-up visits will occur every 12 weeks until no improvement of one or more lines is seen.
* Definition of primary outcome: the 12-week exam visit is the primary outcome visit. For the patching group, after they switch to IO-therapy glasses, the first 12-week exam with IO-therapy glasses is also treated as the primary outcome visit.

SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT (24-31)

24. **Method of Subject Identification and Recruitment**. Does the principal or secondary investigator have ethical/professional access to the names of potential subjects? If not, how will these names be obtained? How will prospective subjects be contacted for recruitment into the study? Attach a copy of any planned advertisements/notices. *Note: The identification and recruitment of subjects must be ethically and legally acceptable and free of coercion. In addition, the recruitment procedure should be designed to facilitate equitable selection of subjects with particular attention paid to the recruitment of study participants of both genders and from different racial/ethnic groups*.

A patient is considered for the study after undergoing an eye examination by an investigator (as part of standard care) that identifies amblyopia meeting the eligibility criteria. For patients who appear eligible for the study following a standard-care examination, the study will be discussed with the child's parent(s) or guardian. Parents or guardians who express an interest in the study will be given a copy of the consent form. Written informed consent will be obtained from the parent or guardian prior to performing any study-specific procedures, which are not part of the patient's routine care. Patients may self-identify, contact investigators and join the study.

A study brochure will be used to recruit subjects.

Electronic health records will also be used to identify eligible study participants at the Eye Institute.

25. **Competing Protocols**. Are there any competing protocols of which you are aware that contain the same or substantially similar eligibility criteria? If a competing protocol(s) exists, the issue of subject selection and recruitment should be addressed. *Note: This section must reflect that the investigator has taken all necessary steps to prioritize subject entry into this protocol in a manner that is in the best interests of the patient*.

N/A

26. **Subject Competency**. Will all adult subjects be competent to give informed consent? If not, describe the likely degree of impairment relative to their ability to consent to participate in research. For those subjects who display questionable impairment, describe how and by whom competency will be assessed. *Note: Patients who are incompetent are considered to be vulnerable and can participate in research only if proxy consent is obtained from their legal representative or a waiver/exception is granted under HHS/FDA Regulations*.

Not Applicable

27. **Process of Informed Consent**. How will the process of informed consent be structured in order to be conducive to rational and thoughtful decision making by the subject/subject's legally authorized representative without any element of coercion or undue influence? *Note: Depending upon the nature of the study, the degree of risk, and the subject population, factors that should be considered in structuring the process of consent include: a) the environment and location where informed consent will be negotiated; b) the amount of time allotted to the process of informed consent; c) the involvement of non-investigators (e.g., technicians) who can help explain the research to the subject/representative; d) utilization of a delayed consent procedure where the subject/representative is encouraged to discuss participation in the study with family, friends, counselors, or other confidants before they sign the consent form; and e) utilization of a re-consent procedure at periodic intervals. This section should clearly document that appropriate attention will be given to the process of informed consent. If children/youth will be subjects, this section should <u>separately</u> address the process of informed assent that should be specifically designed for the age range of the subjects*.

For patients who appear eligible for the study following a "standard-care" examination, the study will be explained to the child's parent(s) or guardian. Parents or guardians who express an interest in the study will be given a copy of the consent form. Written informed consent will be obtained from the parent or guardian prior to performing any study-specific procedures, which are not part of the patient's routine care. All consent process will be in a private room. Parents and children will be given enough time to read consent and ask questions. If they want, they can take a copy of consent to home.

28. **Subject/Representative Comprehension**. How will it be determined that the subject/subject's authorized representative understood the information presented? *Note: All investigators have a legal and an ethical obligation to ensure that the prospective subject/representative has sufficient knowledge and comprehension of <u>all</u> of the elements of informed consent to enable them to make an informed and enlightened decision whether or not to participate or allow participation in research. The elements of informed consent include the purpose of the study, procedures, potential risks, potential benefits, alternatives, and any other information pertinent to informed consent. The fact that an individual is prepared to sign the informed consent form and has no unanswered questions does not necessarily represent sufficient evidence of an adequate level of comprehension. Some investigators, therefore, choose to determine the level of a person's comprehension by*

questioning the individual concerning their understanding of all the elements of informed consent. This section should clearly document that the investigator has an adequate plan in place to assure existence of an acceptable level of comprehension of all the elements of consent.

If children/youth and/or incompetent adults will be subjects, this section should also include a specific plan to assess comprehension during assent.

As a part of the informed consent process, once the parent/guardian has read the informed consent form and decided to participate, the investigator will ask the parent/guardian a series of questions to assess the parent/guardian understanding of the study requirements, risks and benefits. Once the child has read the assent form, or the assent has been read to the child, and the child has decided to participate, the investigator will ask the child a series of question to assess the child's understanding of the study.

We have an assent form for children 7 years old, which uses very simple language to describe the study. They will be given enough time to ask questions.

29. **Information Purposely Withheld**. Will any information be purposely withheld from the subject? If so, state the information to be withheld, justify this non-disclosure, and describe the post-study debriefing of the subject. *Note: Any non-disclosure of the required elements of informed consent must be scientifically justified and minimized to the greatest extent possible. In addition, the alteration in the consent procedure must be approvable under 45 CFR 46.116(d). Non-disclosure is not permitted in FDA-regulated studies except under emergency conditions.*

None.

30. **Consent/Assent Forms**. Specify, for the record, which consent/assent forms will be used in the protocol according to the following categories: adult consent form, parental consent form, proxy consent form, youth assent form (ages 13-17), and/or child assent form (ages 7-12). *Note: During development of these forms, refer to the IRB Guidelines.*

Consent form for parents/guardians and assent form for patients 7 years old.

31. **Documentation of Consent/Assent**. Identify, by name, the investigator(s) and participating optometrists/health care personnel who will document obtainment of informed consent/assent from the subject or the subject's legally authorized representative, i.e., sign the consent/assent form. *Note: Any individual who is authorized by the PI and the IRB to document the obtainment of informed consent/assent from the subject/subject's legally authorized representative must have the necessary clinical expertise as well as sufficient knowledge about the protocol and IRB consent requirements. The PI is responsible for ensuring the obtainment of valid consent/assent from all subjects. Only individuals who are listed in this section are authorized to document consent/assent.*

Jingyun Wang, PhD
Erin Jenewein, OD
Ruth Shoge, OD
Mitchell Scheiman, OD
Michael Gallaway, OD
Jasmine Campbell
Saeed Al Johani
Siva Meiyeppen, OD

LITERATURE REVIEW (32)

32. **References**.

1. Holmes JM, Kraker RT, Beck RW, et al. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. *Ophthalmology* 2003;110:2075-2087.
2. Wallace DK, Edwards AR, Cotter SA, et al. A randomized trial to evaluate 2 hours of daily patching for strabismic and anisometropic amblyopia in children. *Ophthalmology* 2006;113:904-912.
3. BenEzra O, Herzog R, Cohen E, Karshai I, BenEzra D. Liquid crystal glasses: feasibility and safety of a new modality for treating amblyopia. *Archives of ophthalmology* 2007;125:580-581.
4. Spierer A, Raz J, Benezra O, et al. Treating amblyopia with liquid crystal glasses: a pilot study. *Investigative ophthalmology & visual science* 2010;51:3395-3398.
5. Januschowski K, Bechtold TE, Schott TC, et al. Measuring wearing times of glasses and ocular patches using a thermosensor device from orthodontics. *Acta ophthalmologica* 2013;91:e635-640.
6. Repka MX, Kraker RT, Beck RW, et al. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. *Journal of AAPOS : the official publication of the American Association for Pediatric Ophthalmology and Strabismus / American Association for Pediatric Ophthalmology and Strabismus* 2009;13:258-263.

Efficacy of Intermittent Occlusion Therapy Glasses for Amblyopia Dense amblyopia

Parent/Guardian Consent Form

INVITATION
Your child is invited to participate in this research study being conducted at The Eye Institute at Salus University. The National Eye Institute (NEI), part of the federal government, is providing the funding for the study. This study will also be conducted at the Retina Foundation of the Southwest in Dallas, TX and at Indiana University. The information in this consent form is provided to help you decide whether to allow your child to participate. We want to make sure that you also understand that the study involves research. If you have any questions, please do not hesitate to ask.

WHY IS YOUR CHILD ELIGIBLE?
You are being asked to have your child take part in this study because he/she has dense amblyopia (decreased vision) in one eye. Your child is eligible to participate because he/she:

- Is at least 3 and less than 8 years old
- Has been wearing optimal spectacle correction for a minimum of 4 weeks at the time of enrollment
- Has had no amblyopia treatment for at least 6 months
- Has no known allergy to patches or bandage adhesive

If you agree to allow your child to take part in this study, your child will be one of 56 subjects who will be taking part in this multi-center study.

WHAT IS THE PURPOSE OF THIS STUDY?
Amblyopia, known as “lazy eye”, occurs when one eye lacks visual experience at an early age more so than the other eye. This results in one weak eye and another stronger eye. Amblyopia is usually associated with eye turn, unequal vision in the two eyes, or a combination of the two. The currently used treatment is to patch the strong eye to force the use of the weaker eye. This study is designed to evaluate the effectiveness of a new amblyopia treatment, Amblyz™ glasses.

The Amblyz™ glasses regulate the occlusion therapy. They have the ability to become dark at set times and effectively block vision in one of the eyes for 50% of the time they are worn. Therefore, 12 hours of wearing Amblyz™ glasses should be equivalent to wearing an adhesive patch for 6 hours. The primary goal is to determine if wearing Amblyz™ glasses for 12 hours daily can treat amblyopia equally when compared to the standard 6-hour daily patching treatment.

WHAT DOES THIS STUDY INVOLVE?
If you choose to have your child participate in this study, we will ask you for the following information:

- Provide historical information, such as date of birth, gender, ethnicity, prior amblyopia therapy (e.g., glasses, patching, medication, Bangerter filters), history of eye surgery and if your child has an allergy to adhesive skin patches.
- Contact information, such as phone numbers and addresses

We will ask your child to do the following things:

Clinical Testing
Examination procedures include:

- Visual Acuity (vision tested with an eye chart)
- Ocular motility examination (evaluates eye movement and alignment of both eyes)
- Eye examination, within 6 months
- Titmus fly and Randot Preschool Stereoacuity tests (evaluates depth perception)
- Cycloplegic refraction, or refraction after dilating the pupil, if not done within the last 6 months

Randomization
A computer program will be used to decide whether your child will be treated with patching or Amblyz™ glasses. This is similar to flipping a coin to decide on the treatment. You should not agree to have your child be in the study unless you are willing to have your child receive either treatment. Each patient will be randomly assigned to one of two treatment groups:

- Patching treatment group:
    - Your child will wear a patch over the stronger eye 6 hours every day in addition to his/her glasses.
    - You will be given a calendar to write down the total time your child wears the patch each day. You will need to bring this calendar to every study visit.

- Amblyz™ glasses treatment group:
    - Your child will wear the Amblyz™ glasses every day for 12 hours a day. This is equal to a total of 6 hours of occlusion.
    - The Amblyz™ glasses will have a microsensor attached on the glasses for wearing estimation.
    - You will be given a calendar to write down the total time your child wears the glasses each day. You will need to bring this calendar to every study visit.

Phone Call
You will receive a phone call 4 weeks after treatment begins to answer any questions.

Follow-up Visits (each visit, about 1 hour)
Your child will have up to 4 follow-up visits at 12 weeks, 24 weeks, 36 weeks and 48 weeks after treatment has started. Testing at these visits will include the following:
- Visual acuity
- Titmus fly and Randot Preschool Stereoacuity test
- Ocular alignment assessment
- Re-testing of visual acuity in the amblyopic eye

At the Follow-up Visits, your doctor will test your child's vision to check for improvement of the amblyopia.
- If the amblyopia has improved, but not completely, your child's doctor will continue the same treatment and the follow up visits will occur every 12 weeks or until there is no more improvement in the amblyopic eye.

- If the amblyopia has shown little or no improvement:
    - For children in the patching group, your child may be eligible to try the Amblyz™ glasses. This will be determined by your child's doctor.
    - For children in the Amblyz™ glasses group, your child's doctor will discuss continuing treatment or stopping the study.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS YOUR CHILD COULD EXPERIENCE?

Risks of Examination Procedures: The risks and discomforts for the eye examinations will be the same whether or not your child takes part in the study. The drops used to dilate your child's eyes at the first exam may sting for a few seconds. Your child's pupils may remain dilated for the rest of the day, and in some cases may remain dilated for a few days. In very small children, less than 2 years of age, very rarely one or more of the following reactions have been reported to occur: flushed skin, diarrhea, increased heart rate, and seizures.

Risks of Patching: If skin irritation occurs, the parent will be advised to put an emollient on the skin and discontinue use of the patch for a day. Patching could potentially decrease the visual acuity in the stronger eye, although this is almost always reversible. This occurrence is extremely unlikely since the stronger eye will have several hours without occlusion each day. If it does occur, you child's eye doctor will determine what to do. Patching could precipitate the development of an eye turn, although this has been found to be very rare in previous studies and occurs about as often as it does without treatment. If treatment causes the development of an eye turn (e.g., the eyes turning in (esotropia) in child with far-sighted vision (hyperopia), you will be advised to have your child see the investigator as soon as possible.

Risks of Amblyz™ glasses: The children adjust to the flickering of the lens in front of the strong eye easily. At the beginning, Amblyz™ glasses may induce a short-lasting headache or some discomfort. However, just like traditional patching, Amblyz™ glasses could potentially decrease the visual acuity in the stronger eye, although this is almost always reversible. This occurrence is extremely unlikely since the stronger eye will have several hours without occlusion each day and the risk is the same with either the Amblyz™ glasses or traditional patching. If it does occur, you child's eye doctor will determine what to do. So far, there are no reports of significant decrease in the visual acuity in the stronger. As traditional patching treatment may result in eye turn, Amblyz™ glasses could cause the development of an eye turn (strabismus), although this has been found to be very rare in our previous studies. If treatment causes the development of an eye turn, you will be advised to have your child see the investigator as soon as possible.

TheraMon® microsensor: No reported problems or discomfort were indicated by a pilot study using the thermosensor attached to the earpiece of glasses. The thermosensor has been used for a number of years in another study.

Unknown Risks: Although we have tried to list all possible risks and discomforts with this study, there may be others that we do not know about at this time. However, these unknown risks of the treatment would be the same whether your child was part of this study or not.

WHAT ARE THE POSSIBLE BENEFITS TO YOUR CHILD?
You child may or may not benefit from the study. You child's vision in the amblyopic eye may or may not improve from treatments in this study.

WHAT ARE THE POSSIBLE BENEFITS TO SOCIETY?
There is possible benefit if compliance with treatment is increased with the Amblyz™ glasses. The study has potential to help doctors find an equally effective or even better amblyopia treatment for children with amblyopia.

WHAT ARE THE ALTERNATIVES TO PARTICIPATING?
The alternative to taking part in the study is not to take part. There are several options for treating your child's amblyopia. These include:

- Patching
- Eye drops (atropine)
- Fogging lens (Bangerter filter).

WHAT ARE THE FINANCIAL OBLIGATIONS AS A PARTICIPANT?
The study will pay for eye patches, the Amblyz™ glasses and prescription lenses attached to Amblyz™ glasses, which are considered for research. You, or your insurance, will be responsible for the costs that are considered standard-of-care, which includes the follow-up visits. These visits would occur whether or not you are in the study. The enrollment visit, if needed, is at no charge.

WHAT COMPENSATION WILL YOUR CHILD RECEIVE FOR PARTICIPATING?
You will receive $25 per visit for each follow-up visit, and $50 for the 12-week visit after the first time wearing glasses. If enrollment requires a separate exam, $25 will also be paid to you. All payments will be made using ClinCard. For the patching group, the first visit after switching to the Amblyz glasses is the primary outcome visit; for the Amblyz group, the 12-week visit is the primary outcome visit.

WHAT SHOULD YOU DO IN CASE OF EMERGENCY?
If your child is injured or has an adverse reaction because of this study, you should immediately contact one of the personnel listed at the end of this consent form.

HOW WILL YOUR CHILD'S CONFIDENTIALITY BE PROTECTED?
The only persons who will have access to your child's study records are the study personnel, the National Eye Institute, the Salus University Institutional Review Board (IRB), and any other person or agency required by law. The results of clinical tests and therapy performed as part of this study may be included in your child's medical record. The information from this study may be published in scientific journals or presented at scientific meetings and the identity of your child will be kept strictly confidential.

WHAT ARE YOUR CHILD'S RIGHTS AS A STUDY PARTICIPANT?
Your child's participation in this study is voluntary. Your child has rights as a research participant. These rights are explained in *The Rights of Research Participants* that you have been given. If you have any questions concerning your rights, you may contact the Institutional Review Board (IRB), telephone (215) 780-1417.

WHAT WILL HAPPEN IF YOU OR YOUR CHILD DECIDES NOT TO PARTICIPATE?
You or your child may choose not to participate in this study. You may withdraw your consent at any time and discontinue your child's participation without penalty. Your decision will not affect your child's care or relationship with the investigator(s), The Eye Institute, or Salus University. Your decision will not result in any loss of benefits to which your child is entitled.

If any new information develops during the course of this study that may affect your willingness to continue participating, you and your child will be informed immediately.

CONTACTS
If you have any questions or concerns regarding this study, or if any problems arise, you may call the Principal Investigator (Jingyun Wang PhD) at (215-780-1376). You may also ask questions or state concerns regarding you rights as a research subject to Lydia Parke, IRB Administrator, of Salus University's Institutional Review Board, at (215) 780-1417.

DOCUMENTATION OF INFORMED CONSENT

The research study and consent form have been explained to you by:

_____
Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

By signing this form, you are saying that you have had your questions answered, you agree to allow your child to take part in this research study, and that you are legally authorized to consent for your child's participation. **Note: A foster parent is not legally authorized to consent for a foster child's participation.**

_____
Name of Child/Subject

_____ Relation to subject:
Name of Authorized Representative ___Parent ___Legal Guardian

_____ _____
Signature of Authorized Representative Date

Efficacy of Intermittent Occlusion Therapy Glasses for Amblyopia Deprivation amblyopia

Parent/Guardian Consent Form

INVITATION
Your child is invited to participate in this study being conducted at The Eye Institute at Salus University. The National Eye Institute, part of the federal government, is providing the funding for the study. The information in this consent form is provided to help you decide whether to allow your child to participate. We want to make sure that you also understand that the study involves research. If you have any questions, please do not hesitate to ask.

WHY IS YOUR CHILD ELIGIBLE?
You are being asked to have your child take part in this study because he/she has amblyopia (decreased vision) due to previous cataract in one eye. Your child is eligible to participate because he/she:

- Is at least 3 and less than 8 years old
- Has amblyopia associated with pediatric unilateral cataract (congenital or developmental)

If you agree to allow your child to take part in this study, your child will be one of 15 subjects who will be taking part in this multi-center study.

WHAT IS THE PURPOSE OF THIS STUDY?
Amblyopia, known as “lazy eye”, occurs when one eye lacks visual experience at an early age more so than the other eye. This results in one weak eye and another stronger eye. Deprivation amblyopia results from cataracts. The currently used treatment is to patch the strong eye to force the use of the weaker eye. This study is designed to evaluate the effectiveness of a new amblyopia treatment, Amblyz™ glasses.

The Amblyz™ glasses regulate the occlusion therapy. They have the ability to become dark at set times and effectively block vision in one of the eyes for 50% of the time they are worn. Therefore, 12 hours of wearing Amblyz™ glasses should be equivalent to wearing an adhesive patch for 6 hours. The primary objective is to determine if wearing Amblyz™ glasses for 12 hours daily can equally treat amblyopia when compared to the standard 6-hour daily patching treatment.

The purpose of this study is to determine if wearing Amblyz™ glasses can treat deprivation amblyopia.

WHAT DOES THIS STUDY INVOLVE?
If you choose to have your child participate in this study, we will ask you for the following information:

- Provide historical information, such as date of birth, gender, ethnicity, prior amblyopia therapy (e.g., glasses, patching, medicine, Bangerter filters), and history of eye surgery.
- Contact information, such as phone numbers and addresses

We will ask your child to do the following things:

Clinical Testing
Examination procedures include:
- Visual Acuity (vision tested from the eye chart)
- Ocular motility examination (evaluates eye movement and alignment of both eyes)
- Eye Examination, within 6 months
- Titmus fly and Randot Preschool Stereoacuity test (evaluates depth perception)
- Cycloplegic Refraction, or refraction after dilating the pupil, within 6 months

Treatment:
Your child's doctor will decide how many hours a day your child will wear the Amblyz™ glasses depending on your child's visual acuity. Your child will be assigned to wear the Amblyz™ glasses for either 4 hours a day or 12 hours a day.

The Amblyz™ glasses will have a microsensor attached on the glasses for wearing-time estimation.

You will be given a calendar to write down the total time your child wears the patch each day. You will need to bring this calendar to every study visit.

Phone Call
You will receive a phone call 4 weeks after treatment begins to answer any questions.

Follow-up Visits (each visit, about 1 hour)
Your child will have up to 4 follow-up visits at 12 weeks, 24 weeks, 36 weeks and 48 weeks after treatment has started.
Testing at these visits will include the following:
- Visual acuity
- Titmus fly and Randot Preschool Stereoacuity test
- Ocular alignment assessment
- Re-testing of visual acuity in the amblyopic eye

At the Follow-up Visits, your doctor will test your child's vision to check for improvement of the amblyopia.
- If the amblyopia has improved, but not completely, your child's doctor will continue the same treatment and the follow up visits will occur every 12 weeks or until there is no improvement in the amblyopic eye.
- If the amblyopia has shown little or no improvement, your child's doctor will discuss continuing treatment or stopping the study.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS YOUR CHILD COULD EXPERIENCE?

Risks of Examination Procedures: The risks and discomforts for the eye examinations will be the same whether or not your child takes part in the study. The drops used to dilate your child's eyes at the first exam may sting for a few seconds. Your child's pupils may remain dilated for the rest of the day, and in some cases may remain dilated for a few days. In very small children, less than 2 years of age, very rarely one or more of the following reactions have been reported to occur: flushed skin, diarrhea, increased heart rate, and seizures.

Risks of Amblyz™ glasses: The children adjust to the flickering of the lens in front of the strong eye easily. At the beginning, Amblyz™ glasses may induce a short-lasting headache or some discomfort. However, just like traditional patching, Amblyz™ glasses could potentially decrease the visual acuity in the stronger eye, although this is almost always reversible. This occurrence is extremely unlikely since the stronger eye will have several hours without occlusion each day and the risk is the same with either the Amblyz™ glasses or traditional patching. If it does occur, you child's eye doctor will determine what to do. So far, there are no reports of significant decrease in the visual acuity in the stronger. As traditional patching treatment may result in eye

turn, Amblyz™ glasses could precipitate the development of an eye turn, although this has been found to be very rare in our previous studies and indistinguishable from the natural history of eye turn. If treatment precipitates the development of an eye turn, the parent will be advised to have the patient see the investigator as soon as possible.

TheraMon® microsensor: No reported problems or discomfort were indicated by a pilot study using the thermosensor attached to the earpiece of glasses. The thermosensor has been used in another study for a number of years.

Unknown Risks: Although we have tried to list all possible risks and discomforts with this study, there may be others that we do not know about at this time. However, these unknown risks of the treatment would be the same whether your child was part of this study or not.

WHAT ARE THE POSSIBLE BENEFITS TO YOUR CHILD?
You child may or may not benefit from the study. You child's vision in the amblyopic eye may or may not improve from treatments in this study.

WHAT ARE THE POSSIBLE BENEFITS TO SOCIETY?
There is possible benefit if compliance with treatment is increased with the Amblyz™ glasses. The study has potential to help doctors find an equally effective or even better amblyopia treatment for children with amblyopia.

WHAT ARE THE ALTERNATIVES TO PARTICIPATING?
The alternative to taking part in the study is not to take part. Another option for treating your child's amblyopia is daily patching the strong eye.

WHAT ARE THE FINANCIAL OBLIGATIONS AS A PARTICIPANT?
The study will pay for the Amblyz™ glasses and prescription lenses attached to Amblyz™ glasses, which are considered for research. You, or your insurance, will be responsible for the costs that are considered standard-of-care, which includes the follow-up visits. These visits would occur whether or not you are in the study. The enrollment visit, if needed, is at no charge.

WHAT COMPENSATION WILL YOUR CHILD RECEIVE FOR PARTICIPATING?
You will receive a $25 gift card per visit for each follow-up visit. If enrollment requires a separate exam, $25 will also be paid to you.

WHAT SHOULD YOU DO IN CASE OF EMERGENCY?
If your child is injured or has an adverse reaction because of this study, you should immediately contact one of the personnel listed at the end of this consent form.

HOW WILL YOUR CHILD'S CONFIDENTIALITY BE PROTECTED?
The only persons who will have access to your child's study records are the study personnel, the National Eye Institute, the Salus University Institutional Review Board (IRB), and any other person or agency required by law. The results of clinical tests and therapy performed as part of this study may be included in your child's medical record. The information from this study may be published in scientific journals or presented at scientific meetings and the identity of your child will be kept strictly confidential.

WHAT ARE YOUR CHILD'S RIGHTS AS A STUDY PARTICIPANT?
Your child's participation in this study is voluntary. Your child has rights as a research participant. These rights are explained in *The Rights of Research Participants* that you have been given. If you have any questions concerning your rights, you may contact the IRB Administrator of the IRB at (215) 780-1417.

WHAT WILL HAPPEN IF YOU OR YOUR CHILD DECIDES NOT TO PARTICIPATE?
You or your child may choose not to participate in this study. You may withdraw your consent at any time and discontinue your child's participation without penalty. Your decision will not affect your child's care or relationship with the investigator(s), The Eye Institute, or Salus University. Your decision will not result in any loss of benefits to which your child is entitled.

If any new information develops during the course of this study that may affect your willingness to continue participating, you and your child will be informed immediately.

CONTACTS
If you have any questions or concerns regarding this study, or if any problems arise, you may call the Principal Investigator (Jingyun Wang, PhD) at (215-780-1376). You may also ask questions or state concerns regarding you rights as a research subject to Lydia Parke, IRB Administrator, of Salus University's Institutional Review Board, at (215) 780-1417.

DOCUMENTATION OF INFORMED CONSENT

The research study and consent form have been explained to you by:

_____
Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

By signing this form, you are saying that you have had your questions answered, you agree to allow your child to take part in this research study, and that you are legally authorized to consent for your child's participation.
Note: A foster parent is not legally authorized to consent for a foster child's participation.

_____
Name of Child/Subject

_____ Relation to subject:
Name of Authorized Representative ___Parent ___Legal Guardian

_____ _____
Signature of Authorized Representative Date

Efficacy of Intermittent Occlusion Therapy Glasses for Myopic Anisometropic Amblyopia

Parent/Guardian Consent Form

INVITATION

Your child is invited to participate in this study being conducted at The Eye Institute at Salus University. The National Eye Institute, part of the federal government, is providing the funding for the study. The information in this consent form is provided to help you decide whether to allow your child to participate. We want to make sure that you also understand that the study involves research. If you have any questions, please do not hesitate to ask.

WHY IS YOUR CHILD ELIGIBLE?

You are being asked to have your child take part in this study because he/she has myopic anisometropic amblyopia. Your child is eligible to participate because he/she:

- Is at least 3 and less than 8 years old
- Has myopic anisometropic amblyopia
- Has been wearing glasses for a minimum of four weeks
- Has had no amblyopia treatment in the past 3 months
- If you agree to allow your child to take part in this study, your child will be one of 10 subjects who will be taking part in this study.

WHAT IS THE PURPOSE OF THIS STUDY?

Amblyopia, known as “lazy eye”, occurs when one eye lacks visual experience at an early age more so than the other eye. This results in one weak eye and another stronger eye. The currently used treatment is to patch the strong eye to force the use of the weaker eye. This study is designed to evaluate the effectiveness of a new amblyopia treatment, Amblyz™ glasses.

The Amblyz™ glasses regulate the occlusion therapy. They have the ability to become dark at set times and effectively block vision in one of the eyes for 50% of the time they are worn. Therefore, 12 hours of wearing Amblyz™ glasses should be equivalent to wearing an adhesive patch for 6 hours. The primary objective is to determine if wearing Amblyz™ glasses for 12 hours daily can equally treat amblyopia when compared to the standard 6-hour daily patching treatment.

The purpose of this study is to determine if wearing Amblyz™ glasses can treat myopic anisometropic amblyopia.

WHAT DOES THIS STUDY INVOLVE?

If you choose to have your child participate in this study, we will ask you for the following information:

- Historical information, such as date of birth, gender, ethnicity, prior amblyopia therapy (e.g., glasses, patching, medicine, Bangerter filters), and history of eye surgery.
- Your contact information, such as phone numbers and addresses

We will ask your child to do the following things:

Clinical Testing
Examination procedures include:
- Visual Acuity (vision tested from the eye chart)
- Ocular motility examination (evaluates eye movement and alignment of both eyes)
- Eye Examination, within 6 months
- Titmus fly and Randot Preschool Stereoacuity test (evaluates depth perception)
- Cycloplegic Refraction, or refraction after dilating the pupil, within 6 months

Treatment:
Your child's doctor will decide how many hours a day your child will wear the AmblyzTM glasses. Your child may wear the AmblyzTM glasses for 4 hours/day or 12 hours/day depending on your child's visual acuity.

The Amblyz™ glasses will have a microsensor attached on the glasses for wearing-time estimation.

You will be given a calendar to write down the total time your child wears the Amblyz™ glasses each day. You will need to bring this calendar to every study visit.

Phone Call
You will receive a phone call 4 weeks after treatment begins to answer any questions.

Follow-up Visits (each visit, about 1 hour)
Your child will have up to 4 follow-up visits at 12 weeks, 24 weeks, 36 weeks and 48 weeks after treatment has started.
Testing at these visits will include the following:
- Visual acuity
- Titmus fly and Randot Preschool Stereoacuity test
- Ocular alignment assessment
- Re-testing of visual acuity in the amblyopic eye

At the Follow-up Visits, your doctor will test your child's vision to check for improvement of the amblyopia.
- If the amblyopia has improved, but not completely, your child's doctor will continue the same treatment and the follow up visits will occur every 12 weeks or until there is no improvement in the amblyopic eye.
- If the amblyopia has shown little or no improvement, your child's doctor will discuss continuing treatment or stopping the study.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS YOUR CHILD COULD EXPERIENCE?

Risks of Examination Procedures: The risks and discomforts for the eye examinations will be the same whether or not your child takes part in the study. The drops used to dilate your child's eyes at the first exam may sting for a few seconds. Your child's pupils may remain dilated for the rest of the day, and in some cases may remain dilated for a few days. In very small children, less than 2 years of age, very rarely one or more of the following reactions have been reported to occur: flushed skin, diarrhea, increased heart rate, and seizures.

Risks of Amblyz™ glasses: The children adjust to the flickering of the lens in front of the strong eye easily. At the beginning, Amblyz™ glasses may induce a short-lasting headache or some discomfort. However, just like traditional patching, Amblyz™ glasses could potentially decrease the visual acuity in the stronger eye, although this is almost always reversible. This occurrence is extremely unlikely since the stronger eye will have several

hours without occlusion each day and the risk is the same with either the Amblyz™ glasses or traditional patching. If it does occur, you child's eye doctor will determine what to do. So far, there are no reports of significant decrease in the visual acuity in the stronger. As traditional patching treatment may result in eye turn, Amblyz™ glasses could precipitate the development of an eye turn, although this has been found to be very rare in our previous studies and indistinguishable from the natural history of eye turn. If treatment precipitates the development of an eye turn, the parent will be advised to have the patient see the investigator as soon as possible.

TheraMon® microsensor: No reported problems or discomfort were indicated by a pilot study using the thermosensor attached to the earpiece of glasses. The thermosensor has been used in another study for a number of years.

Unknown Risks: Although we have tried to list all possible risks and discomforts with this study, there may be others that we do not know about at this time. However, these unknown risks of the treatment would be the same whether your child was part of this study or not.

WHAT ARE THE POSSIBLE BENEFITS TO YOUR CHILD?
You child may or may not benefit from the study. You child's vision in the amblyopic eye may or may not improve from treatments in this study.

WHAT ARE THE POSSIBLE BENEFITS TO SOCIETY?
There is possible benefit if compliance with treatment is increased with the Amblyz™ glasses. The study has potential to help doctors find an equally effective or even better amblyopia treatment for children with amblyopia.

WHAT ARE THE ALTERNATIVES TO PARTICIPATING?
The alternative to taking part in the study is not to take part. Another option for treating your child's amblyopia is daily patching the strong eye.

WHAT ARE THE FINANCIAL OBLIGATIONS AS A PARTICIPANT?
The study will pay for the Amblyz™ glasses and prescription lenses attached to Amblyz™ glasses, which are considered for research. You, or your insurance, will be responsible for the costs that are considered standard-of-care, which includes the follow-up visits. These visits would occur whether or not you are in the study. The enrollment visit, if needed, is at no charge.

WHAT COMPENSATION WILL YOUR CHILD RECEIVE FOR PARTICIPATING?
You will receive a $25 gift card per visit for each follow-up visit. If enrollment requires a separate exam, $25 will also be paid to you.

WHAT SHOULD YOU DO IN CASE OF EMERGENCY?
If your child is injured or has an adverse reaction because of this study, you should immediately contact one of the personnel listed at the end of this consent form.

HOW WILL YOUR CHILD'S CONFIDENTIALITY BE PROTECTED?
The only persons who will have access to your child's study records are the study personnel, the National Eye Institute, the Salus University Institutional Review Board (IRB), and any other person or agency required by law. The results of clinical tests and therapy performed as part of this study may be included in your child's medical record. The information from this study may be published in scientific journals or presented at scientific meetings and the identity of your child will be kept strictly confidential.

WHAT ARE YOUR CHILD'S RIGHTS AS A STUDY PARTICIPANT?
Your child's participation in this study is voluntary. Your child has rights as a research participant. These rights are explained in *The Rights of Research Participants* that you have been given. If you have any questions concerning your rights, you may contact the IRB Administrator of the IRB at (215) 780-1417.

WHAT WILL HAPPEN IF YOU OR YOUR CHILD DECIDES NOT TO PARTICIPATE?
You or your child may choose not to participate in this study. You may withdraw your consent at any time and discontinue your child's participation without penalty. Your decision will not affect your child's care or relationship with the investigator(s), The Eye Institute, or Salus University. Your decision will not result in any loss of benefits to which your child is entitled.

If any new information develops during the course of this study that may affect your willingness to continue participating, you and your child will be informed immediately.

CONTACTS
If you have any questions or concerns regarding this study, or if any problems arise, you may call the Principal Investigator (Jingyun Wang, PhD) at (215-780-1376). You may also ask questions or state concerns regarding you rights as a research subject to Lydia Parke, IRB Administrator, of Salus University's Institutional Review Board, at (215) 780-1417.

DOCUMENTATION OF INFORMED CONSENT

The research study and consent form have been explained to you by:

_____
Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

By signing this form, you are saying that you have had your questions answered, you agree to allow your child to take part in this research study, and that you are legally authorized to consent for your child's participation.
Note: A foster parent is not legally authorized to consent for a foster child's participation.

_____
Name of Child/Subject

_____ Relation to subject:
Name of Authorized Representative ___Parent ___Legal Guardian

_____ _____
Signature of Authorized Representative Date

Statistical analysis

Descriptive statistics (mean and standard deviation) will be applied to the primary and secondary outcomes. A paired t-test will be applied to analyze visual acuities before and after treatment for each group; an independent t-test will be applied to analyze visual acuity improvement between groups.