Regimens of Intermittent Occlusion Therapy for Amblyopia in Children

NCT02767856

ID: HJW1604

Protocol: 04/09/2019

Informed consent form: 12/18/18

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**.

Recently, liquid-crystal intermittent-occlusion therapy (IO-therapy) glasses, electronic devices, are suggested for effectively treating amblyopia.

In this protocol, we aim to answer the question: What if the IO-therapy glasses were prescribed all day (12-hours) in which the total time of treatment only took 4 weeks instead of the current treatment time (4 hours) in which it takes 12 weeks? In addition, we will estimate the long-term effect of IO-therapy glasses with these regimens.

In this study, we also monitor compliance with IO-therapy glasses. Januschowski et al. (2013) introduced a TheraMon® microsensor (called a "thermosensor" hereafter), typically used in orthodontics, to objectively measure compliance with wearing glasses.[1] This thermosensor conveniently fits IO-therapy glasses.

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.

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.[2, 3]

Non-randomized studies reported that IO-therapy glasses yield an improvement in the amblyopic eye and offer an effective, alternative treatment.[3, 4] Regimen in these studies depended on physicians' preference. Previously, we hypothesized that 4 hours of IO-therapy would be as effective as 2 hours of continuous patching occlusion. In our almost-completed ongoing clinical trial, 3- to 8-year-old children with untreated moderate unilateral amblyopia were randomized into the 2-hour patching group or the 4-hour IO-therapy glasses group. At the conclusion of the first 12-week treatment interval, visual acuity in the amblyopic eye significantly improved in both groups. There was no statistically significant difference between the two groups (P-value=0.6). Overall, parents reported a high level of enthusiasm with the IO-therapy glasses for daily use, commonly remarking that they were easy to wear. Although the sample size is small, our pilot data support the hypothesis that 4-hours of IO-therapy works just as effectively as 2-hours of continuous patching occlusion in treating amblyopia.(Wang, et al. ARVO abstract, 2015) However, the daily regimen of IO-therapy is uncertain.

Daily regimen of occlusion treatment has been controversial for a long time. Total occlusion time matters. A previous patching study reported a predominantly linear relationship between the total cumulative dose of occlusion and the response over the first 400 hours.[5] An intense occlusion regimen was often suggested previously. Vision in

amblyopic patients improved similarly for the 6-hour patching regimen and the full-time patching regimen; unfortunately, the study did not track compliance in patients.[6] However, using an occlusion dose monitor, another study found those patients with longer time regimen have lower compliance; in other words, patients in both groups ended up with similar actual occlusion time. Therefore, patients with "full-time" or "6-hour" regimen had similar occlusion; i.e. "full-time" regimen did not really function as an intense regimen as we expected. Switching to an intense regimen was reported as effective sometime.[7] For instance, when the amblyopic eye stops improving vision with 2 hours of daily patching, increasing the daily patching dosage to 6 hours results in more improvement compared with continuing 2-hour patching.[7] On the other hand, according to numerous animal studies, total full-time patching of the fellow eye to improve vision in the amblyopic eye does not result in long-term restoration of normal visual acuity in both eyes.[8] Therefore, combining non-occlusion hours with occlusion hours of the fellow eye maybe better for the long-term outcome. The IO-therapy glasses are designed to occlude the fellow eye 50%of the time. Can we use an intense regimen of IO-therapy glasses?

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*.

This is a pilot study. With a computer program with randomized, permuted-block design, 56 patients will be randomized in the two treatment groups with 28 patients in each group.

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, Philadelphia, PA. (new site)

Each site will work on the enrollment until we reach the total goal N=56 patients with **moderate** amblyopia. Enrollment will cease when the total goal is reached.

4. **Gender of the Subjects**.

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

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

Not Applicable

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 to the PEDIG Amblyopia studies. This age range is the most effective age to 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?

The following criteria must be met for the patient to be enrolled in the study:

1. Age 3 to < 8 years
2. Unilateral 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
     - >0.50 D difference between eyes in astigmatism in any meridian
3. Amblyopic eye has no myopia (> -0.25 D spherical equivalent).
4. 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 20/40 and 20/80 inclusive
     - Visual acuity in the sound eye 20/32 or better
     - Inter-eye acuity difference ≥ 2 logMAR lines (i.e., amblyopic eye acuity at least 2 lines worse than sound eye acuity)
5. No previous amblyopia treatment within 6 months.
6. 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:
   - <u>Requirements for spectacle correction:</u>
     - For patients meeting criteria for only strabismus
       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
       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
     - <u>Spectacles meeting above criteria must be worn either:</u>
       i. for 4 weeks immediately prior to enrollment, or
       ii. until visual acuity in amblyopic eye is stable (defined as two consecutive visual acuity measurements at least 4 weeks apart with no improvement of one line or more)
       iii. An acuity measurement done any of the following ways may be considered the first of two consecutive measurements: 1) in current glasses, 2) in trial frames with full correction of hypermetropia with cycloplegia, or 3) in new glasses.
7. **Prior to the time of enrollment, spectacles had to provide optimal correction for a minimum of 12 weeks or until stability of visual acuity was documented (no improvement in amblyopic eye visual acuity at 2 consecutive visits at least 4 weeks apart).**
8. Ocular examination within 6 months prior to enrollment.
9. Gestational age > 34 weeks and birth weight > 1500 grams
10. Parent willing to accept randomization
11. Parent willing to be contacted and has access to phone
12. Parent does not anticipate relocation outside area within study period.

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

   - Amblyopic eye has myopia worse than -3.00 D spherical equivalent.
   - Prior intraocular or refractive surgery

- Ocular pathologies that impact vision
- Cognitive impairment that prohibits accurate data collection

10. **Vulnerable Subjects**.

Children will be included in the study because amblyopia is an eye disease that occurs in children.

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, and history of eye surgery.

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

Clinical Testing before randomization

Examination procedures include:

1. **Visual Acuity** within 7 days prior to 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 prior to enrollment

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

3. **Ocular Examination** within 6 months prior to enrollment

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 prior to enrollment
5. **Cycloplegic Refraction** within 6 months prior to enrollment

Cycloplegic refraction using cyclopentolate 1%

Randomized Treatment Groups

Eligible patients will be randomized to one of two treatment regimens:

- IO-therapy glasses standard regimen group (Standard group): 4-hour daily IO-therapy glasses
- IO-therapy glasses intense regimen group (Intense group): 12-hour daily IO-therapy glasses

Notes

1. The study will provide a pair of IO-therapy glasses, which will have a TheraMon® microsensor attached.[1]
2. If a patient is noncompliant with treatment, the parents should be encouraged to persist with their efforts to encourage compliance.
3. Prior to deviating from the treatment protocols or prescribing non-protocol treatment, the situation should be discussed with the PI.
4. 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 follow “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.

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.

Follow-up Interactions

After randomization, all patients will have the following study visits/interactions:

Telephone Call

- To answer any questions and to encourage compliance with treatment, each patient will be contacted by the research coordinator via telephone at 1 week following treatment.

Primary Outcome Visit (both 4 ± 1 weeks & 12 ± 1 weeks after patient received glasses)

The primary outcome visit will occur at 4 ± 1 weeks for the Intense Group & at 12 ± 1 weeks for the Standard Group. In addition, we ask the Standard Group visit back at 4 ± 1 weeks for comparing with the Intense Group.

Testing will include the following:

1. **Visual acuity**
   - Measured in each eye (weaker 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. Microsensor 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 will transfer the data to a PC for storage; wearing times will be evaluated using the TheraMon® Software and compared to the wearing times protocol.

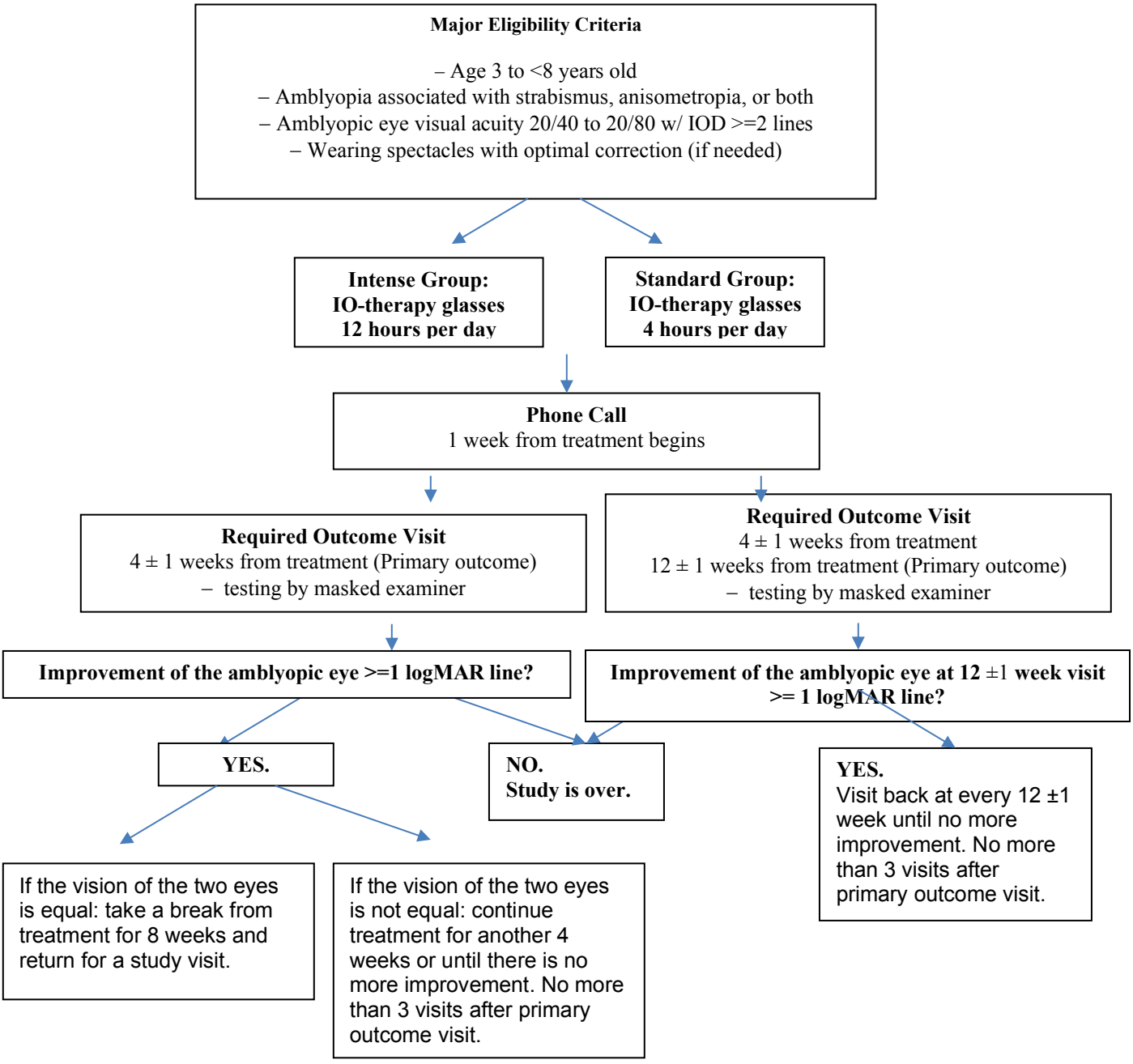
Test	**Visit / Interaction**			
	Enrollment	*1 wk phone call*	*Required visits* *4 ±1 wk for both groups* *& 12 ±1 wk (for Standard Group)* *(by masked examiner)*	**Follow-Up Visits after the Primary Outcome**

Telephone call		X		
Distance acuity each eye*	X		X	X
Ocular alignment	X		X	X
Titmus Fly	X		X	X
Randot Preschool Test	X		X	X
Compliance reading on sensor and calendar			X	X

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

Follow-Up Visits with the same tests as the Primary outcome visit after the Primary Outcome (see flow chart)

Study Summary Flow Chart



Primary Analysis for Safety

Sound Eye Acuity Data

The loss of 2 or more lines in sound eye visual acuity from baseline to the masked exam at the primary outcome visit will be tabulated for each treatment group.

Stereoacuity

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

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).[3] Because the IO therapy glasses are a novel device used to treat severe amblyopia, we are uncertain how many 3 to <8 year-old patients will drop out from the study. According to an average 15% dropout rate in previous amblyopia studies[6, 9], 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 Amblyz IO-therapy glasses and TheraMon® thermosensor. We attach the medical device form of Amblyz glasses and thermosensor. Amblyz 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 file cabinet, which 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.

Risks of Amblyz 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 in the visual acuity (2 lines logMAR) in the sound eye reported. [3]

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. too 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[1] 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 46.404, 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 the 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 effective or even better regimen of IO-therapy amblyopia treatment for children.

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 alternatives available are 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 research must be at least 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.*

Compared to the benefit that we may find an effective regimen of IO-therapy for amblyopia treatment, risk associated with this study is minimum.

FINANCIAL OBLIGATIONS AND COMPENSATION (21-23)

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

The optical corrections for IO-therapy glasses will be provided by the study at no cost. IO-therapy glasses will be loaned to patients. The study will pay for follow-up visits and testing related to this study. There are no financial obligations for the subject.

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.*

Subjects will not pay extra money.

23. **Financial Compensation for Participation**.

The parent/guardian of each child will be compensated $25 for each follow-up visit, and $50 for the primary outcome visit. $25 for completion of the enrollment visit, if needed. For patients remaining in follow-up after the primary outcome visit, $25 will be paid for each visit up to $150. No payment for visits after a total of $150 payment. If there are extenuating circumstances, additional funds may be provided for travel if expenses exceed $25 and the patient will be unable to complete the visit without reimbursement of travel expenses. All payments will be made in the end each completed visit. All payments will be made using ClinCard.

Testing	Visit Schedule	Time	Payment
Enrollment testing (if separate visit needed)		30-60 mins	$25
Required Visits	Standard Group: • 4-week • 12-week (primary outcome)	30-60 mins	$50, each visit
	Intense Group: • 4-week (primary outcome)	30-60 mins	$50
For subjects whose vision improves, follow-up visits after the Primary Outcome	First visit after primary	30-60 mins	$25
	Second visit after primary	30-60 mins	$25 (except for the Standard Group
	Third visit after primary	30-60 mins	$25 (except for the Stanard Group
Total	Maximum 5 visits for the Intense Group and 6 visits for the Standard Group.		No more than $150 total

*For the standard group, the 4 week visit is also considered the primary outcome.

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.

We also have a flyer, which will be emailed or sent to clinicians to advertise the study.

St. Christopher's Hospital for Children is a site that helps with identifying eligible patients. They will distribute flyers to patients who meet the criteria for the study and instruct them to contact investigators if they are interested.

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 brochure and 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 of the 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 the informed consent document home to decide if they want to continue.

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 <u>all</u> 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 <u>all</u> 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 questions 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 all subjects 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
Siva Meiyeppen, OD
Jasmine Campbell
Saeed Al Johani

LITERATURE REVIEW (32)

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Parent/Guardian Consent Form

Intense vs Standard Regimens of Intermittent Occlusion Therapy for Unilateral Moderate Amblyopia in Children

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) is providing the funding for the study. NEI is part of the federal government. 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?

Your child is eligible to participate because he/she has amblyopia ("lazy eye") in one eye and:

- Is 3 to < 8 years of age
- Has been wearing optimal spectacle correction for a minimum of 12 weeks at the time of enrollment or visual acuity in the amblyopic eye did not change in two visits (at least 4-week apart).
- Has had no amblyopia treatment for at least 6 months
- Has had an eye examination that includes eye health in the last 6 months

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 research.

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 one stronger eye. Amblyopia is usually associated with an eye turn, unequal vision in the two eyes, or a combination of the two. One of the currently-used treatments is occlusion therapy, in which an eye patch is worn over 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, 4 hours of wearing Amblyz™ glasses should be equivalent to wearing an adhesive-eye patch for 2 hours.

It is not clear how much occlusion treatment of the good eye is needed to improve the visual acuity in the amblyopic (weak) eye. Amblyz™ glasses allow us to determine if the child is wearing the glasses for the appropriate time. The goal of this study is to compare two treatments with Amblyz™ glasses.

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, medication, Bangerter filters), and history of eye surgery
- Contact information, such as phone numbers and addresses

Enrollment exam:

- vision tested with an eye chart
- evaluate how well your child's eyes line up with each other
- evaluate depth perception
- Refraction with eye drops if not done within the last 6 months

Randomized Treatment Groups

All children will wear newly-developed Amblyz™ glasses. The Amblyz™ glasses will have a thermosensor attached on the glasses to estimate how long they are being worn.

A computer program will be used to decide which treatment your child will receive. 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 child will be randomly assigned to one of the following treatment groups:

- Standard group: 4-hours daily Amblyz™ glasses (total occlusion time 2 hours) for 12 weeks
- Intense group: 12-hours daily Amblyz™ glasses (total occlusion time 6 hours) for 4 weeks

Phone Call

You will receive a phone call 1 week after treatment begins to answer any questions you might have.

Follow-up visits (each visit, about 1 hour):

If your child is in the Intense Group, your child is required to come back for one visit at 4 weeks. If your child is in the Standard Group, your child is required to come back at both 4 weeks and 12 weeks for testing. Please bring the Amblyz™ glasses with you to all visits.

Testing at these visits will include the following:

- Vision tested using an eye chart
- Depth perception
- how well your child's eye line up with each other

If the amblyopia has improved, but not completely, your child's doctor will continue the same treatment; your child will have no more than 3 follow-up visits for this study.

If the amblyopia is improved and two eyes are equal in the Intense Group, your child will stop the treatment for 8 weeks and return for a follow-up visit to check if your child's vision is stable.

If the amblyopia has shown little or no improvement, the study is over.

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.

Amblyz™ glasses: Children usually 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. Just like traditional patching, Amblyz™ glasses could potentially decrease the visual acuity in the stronger eye, although this is almost always reversible. However, 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, in studies like this one, no significant decrease in the visual acuity in the sound eye has been reported. 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 the 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?
Your child may or may not benefit from the study. You child's vision in the amblyopic eye may or may not improve with treatments in this study.

WHAT ARE THE POSSIBLE BENEFITS TO SOCIETY?
There is potential benefit in that compliance with treatment may be increased with the Amblyz™ glasses. The study has potential to help doctors find an equally effective or even better 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, or fogged lens.

WHAT ARE THE FINANCIAL OBLIGATIONS AS A PARTICIPANT?
There are no financial obligations for participating. The enrollment exam (if needed), the 4-week study visit and the 12-week study visit are research visits.

The study will provide the Amblyz™ glasses, which are used in this study. You must bring the Amblyz™ glasses back when your involvement in this study finishes.

WHAT COMPENSATION WILL YOUR CHILD RECEIVE FOR PARTICIPATING?
You will receive $50 for the first follow-up visit and $25 for all other study visits. All payments will be made using ClinCard. For the intense group, the 4-week visit is the primary outcome; for the standard group, both the 4-week and the 12-week visit are the primary outcome.

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?
Your study data will be handled as confidentially as possible. If results of this study are published or presented, individual names and other personally identifiable information will not be used. There are some reasons why people other than the researchers may need to see information you provided as part of the study. This includes organizations responsible for making sure the research is done safely and properly, including:

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Salus University Institutional Review Board;

If this study is related to your medical care, and with your permission, your study-related information may be placed in your clinic record.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

WHAT ARE YOUR CHILD'S RIGHTS AS A 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 your rights as a research subject to Lydia Parke, IRB Administrator, of the 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.

With total hours during treatment recorded with microsensor and improved visual acuity in the amblyopic eye, we can estimate the dose-response relationship for IO-therapy.