
Title : Seeing is Learning: Vision in Rural Chinese Primary Schools
Approval Period: 06/30/2016 - 06/30/2017

Continuing Review Form

1. Participant Enrollment

- a. **Number of participants entered (or number of specimens examined or charts reviewed) since the beginning of study. If this is a combined VA-Stanford study, in addition indicate how many of the participants (or number of VA specimens examined or VA charts reviewed) enrolled with a VA consent. If this is a multi-site study, in addition to the number of participants enrolled locally, include the number of participants enrolled study-wide.**

19,997

- b. **Number of males, # of females.**

Male: 10,199
Female: 9798

- c. **Minority status of participants entered since beginning of study.**

Less than one percent of participants belong to an ethnic minority.

- d. **Number of children (less than 18 years) entered since beginning of study.**

19,995

- e. **Number of other potentially vulnerable subjects (if applicable) entered since the beginning of study, including prisoners, pregnant women, economically and educationally disadvantaged, decisionally impaired and homeless people.**

19,995. The children in this study are generally economically and educationally disadvantaged when compared to their urban counterparts. Urban residents in China enjoy a much higher standard of living than those in rural areas. All subjects in this research are from rural areas.

2. Study Problems/Complications

- a. **Number of withdrawals of participants from the research (both participant and investigator initiated) since the beginning of the research study. Provide reasons for the withdrawals.**

0. Certainly there are students that have chosen not to wear their glasses, but we don't classify that as a "withdrawal."

- b. **Number of participants lost to follow-up since the beginning of the study.**

In the past year we have not sought to follow up with patients in the study

- c. **Provide a narrative summary of the adverse events since the last renewal. Indicate whether adverse events experienced by participants are different from those originally anticipated.**

There are no adverse effects to report in the last renewal period.

- d. **Provide a narrative summary (not a list) of the unanticipated problems involving risks to participants or others that have occurred in the research in the past year. Confirm that all events and information that require prompt reporting to the IRB**

/research/documents/Events-Info-Report-to-IRB_GUI03P13.pdf (guidance GUI-P13) have been

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reported as required.

No unanticipated problems involving risks have occurred over the past year.

- e. Provide a narrative summary of all relevant reports received in the past year whether or not the report has been previously submitted to the IRB. Summarize adverse event reports, audit results, and any other reports. Include corrective actions taken as a result of any audits.**

N/A

- f. Complaints about the research in the past year.**

N/A

- g. Noncompliance: Has there been any agency, institutional, or other inquiry into noncompliance in the study, or any finding of noncompliance concerning a member of the research team? If yes, please explain.**

N/A

3. Study Assessment

- a. Provide a narrative summary of any interim findings from your data in the past year.**

We compared glasses usage rates in the information only group vs the control group, to measure the impact of the information campaign on vision care uptake. We have also included the data from this sample into a meta analysis of vision care studies.

- b. Provide a narrative summary of any recent relevant literature.**

NA

- c. Attach Data Safety Monitoring Reports in section 16 received in the past year which have not previously been submitted to the IRB.**

N/A

- d. Provide a narrative summary of benefits experienced by participants in the past year.**

We have shown in this trial and in another impact evaluation that glasses wear can improve academic performance among myopic children. We are confident that with continued wear these effects remain and may even be cumulative.

- e. Provide an assessment of whether the relationship of risks to potential benefits has changed.**

N/A

4. Description of remainder of project:

- a. N Is the study open to enrollment?**
- b. Y Is the study permanently closed to enrollment of new participants?**
- c. Y Have all participants completed all research-related interventions?**
- d. N Are you still engaged in research-related intervention(s)? If yes, please describe.**

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e. N Do you wish to renew this study only for long term follow-up?

f. Y Are you only doing data analysis?

5. Potential Conflict of Interest

N Is there a change in the conflicting interest status of this protocol?

6. Protocol Changes

Please note that if these changes involve changes to Radiation Safety or Biosafety, the IRB will hold its approval until Radiation Safety or Biosafety forwards its approval to the IRB. Use track changes IF revising consent, assent or HIPAA.

- Summarize all of the proposed changes to the protocol application including consent form changes.

- Indicate Level of Risk

- Describe any other changes.

| Protocol Director | | | | |
|--------------------------------|--------------------------|-------------------------------------------------|----------------------------|---------------------------------------|
| Name Scott D Rozelle | | Degree (program/year if student) Ph D | | Title Senior Fellow |
| Dept FSI - FSE | Mail Code 6055 | Phone 650-724-6402 | Fax 650-723-6530 | E-mail rozelle@stanford.edu |
| CITI Training current | | | | Y |

| Admin Contact | | | | |
|------------------------------|--------------------------|-----------------------------------------------|------------|----------------------------------------------|
| Name Alexis Medina | | Degree (program/year if student) MA | | Title Social Science Research Asst |
| Dept FSI - FSE | Mail Code 6055 | Phone 561-445-8685 | Fax | E-mail amedina5@stanford.edu |
| CITI Training current | | | | Y |

| Investigator | | | | |
|---------------------|------------------|-----------------------------------------|------------|---------------|
| Name | | Degree (program/year if student) | | Title |
| Dept | Mail Code | Phone | Fax | E-mail |

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CITI Training current

Other Contact

| Name | Degree (program/year if student) | | Title |
|------------------------|----------------------------------|--|-----------------|
| Matthew Werner Boswell | MA | | Project Manager |

| Dept | Mail Code | Phone | Fax | E-mail |
|-----------|-----------|----------------|-----|--------------------|
| FSI - FSE | 6055 | (650) 724-3920 | | kefka@stanford.edu |

CITI Training current Y

Academic Sponsor

| Name | Degree (program/year if student) | | Title |
|------|----------------------------------|--|-------|
| | | | |

| Dept | Mail Code | Phone | Fax | E-mail |
|------|-----------|-------|-----|--------|
| | | | | |

CITI Training current

Other Personnel

Participant Population(s) Checklist

Yes/No

- Children (under 18) Y
- Pregnant Women and Fetuses N
- Neonates (0 - 28 days) N
- Abortuses N
- Impaired Decision Making Capacity N
- Cancer Subjects N
- Laboratory Personnel N
- Healthy Volunteers N
- Students Y
- Employees N
- Prisoners N
- Other (i.e., any population that is not specified above) Y

Study Location(s) Checklist

Yes/No

- Stanford University Y
- Clinical & Translational Research Unit (CTRU)
- Stanford Hospital and Clinics
- Lucile Packard Children's Hospital (LPCH)
- VAPAHCS (Specify PI at VA)
- Other (Click ADD to specify details) Y

| Location / | Location | Contact | Contact | Contact Email | Permission | Enga |
|------------|----------|---------|---------|---------------|------------|------|
| | | | | | | |

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| Country | | Name | Phone | | ? | ged? |
|---------------------------------------------------|--|--------------|----------------|-------------------------|---|------|
| 360 schools in NW China (Gansu, Ningxia, Shaanxi) | | Yaojiang Shi | 86-29-88308337 | syj8882002@yahoo.com.cn | Y | N |

General Checklist

Multi-site

Yes/No

- Is this a multi-site study? A multi-site study is generally a study that involves one or more medical or research institutions in which one site takes a lead role.(e.g., multi-site clinical trial)

N

Collaborating Institution(s)

Yes/No

- Are there any collaborating institution(s)? A collaborating institution is generally an institution that collaborates equally on a research endeavor with one or more institutions.

Y

| Institution Name | Contact Name | Contact Phone | Contact Email | Permission? | Engaged? |
|----------------------------------------------------|---------------|----------------|--------------------------|-------------|----------|
| Ctr for Chinese Ag. Policy, Chinese Academy of Sci | Linxiu Zhang | 86-10-64889834 | lxzhang.ccap@igsnr.ac.cn | Y | N |
| Renmin University | Xiaopeng Pang | | | Y | N |

Cancer Institute

Yes/No

- Cancer-Related Studies (studies with cancer endpoints), Cancer Subjects (e.g., clinical trials, behavior/prevention) or Cancer Specimens (e.g., blood, tissue, cells, body fluids with a scientific hypothesis stated in the protocol).

N

Clinical Trials

Yes/No

- Investigational drugs, biologics, reagents, or chemicals? N
- Commercially available drugs, reagents, or other chemicals administered to subjects (even if they are not being studied)? Y
- Investigational Device / Commercial Device used off-label? N
- IDE Exempt Device (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved

N

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Devices)

- This study will be registered on N
<https://stanfordmedicine.box.com/s/ehpld4l0jresrtbvmd3qbg7flrc78ljw> clinicaltrials.gov?
- Is <https://stanfordmedicine.box.com/s/z92zongt53mz45wdct08z4cq0j95r2xz> Stanford responsible for registration under HHS regulation or NIH policy?
NCT#

Tissues and Specimens**Yes/No**

- Human blood, cells, tissues, or body fluids (tissues)? N
- Tissues to be stored for future research projects? N
- Tissues to be sent out of this institution as part of a research agreement? For guidelines, please see <https://sites.stanford.edu/ico/mtas> N

Biosafety (APB)**Yes/No**

- Are you submitting a recombinant DNA vector or Human Gene Transfer investigation using biological agents? If yes, please complete and attach the Gene Transfer Protocol Application Supplemental Questions to section 16 of the eProtocol application. N
- Are you submitting a Human study using biohazardous/infectious agents? If yes, refer to the <http://www.stanford.edu/dept/EHS/prod/researchlab/bio/index.html> Administrative Panel on BioSafety website prior to performing studies. N
- Are you submitting a Human study using samples from subjects that are known or likely to contain biohazardous/infectious agents? If yes, refer to the <http://web.stanford.edu/dept/EHS/prod/researchlab/bio/index.html> Administrative Panel on BioSafety website prior to performing studies. N

Human Embryos or Stem Cells**Yes/No**

- Human Embryos or Gametes? N
- Human Stem Cells (including hESC, iPSC, cancer stem cells, progenitor cells) N

Veterans Affairs (VA)**Yes/No**

- The research recruits participants at the Veterans Affairs Palo Alto Health Care System(VAPAHCS). N
- The research involves the use of VAPAHCS non-public information to identify or contact human research participants or prospective subjects or to use such data for research purposes. N
- The research is sponsored (i.e., funded) by VAPAHCS. N
- The research is conducted by or under the direction of any employee or agent of VAPAHCS (full-time, part-time, intermittent, consultant, without compensation (WOC), on-station fee-basis, on-station contract, or on-station sharing agreement basis) in N

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connection with her/his VAPAHCS responsibilities.

- The research is conducted using any property or facility of VAPAHCS. N

Equipment

Yes/No

- Use of Patient related equipment? If Yes, equipment must meet the standards established by Hospital Instrumentation and Electrical Safety Committee (650-725-5000) N
- Medical equipment used for human patients/subjects also used on animals? N
- Radioisotopes/radiation-producing machines, even if standard of care? N
http://www.stanford.edu/dept/EHS/prod/researchlab/radlaser/Human_use_guide.pdf More Info

Payment

Yes/No

- Subjects will be paid/reimbursed for participation? See payment considerations. N

Funding

Yes/No

- Training Grant? N
- Program Project Grant? N
- Federally Sponsored Project? N
- Industry Sponsored Clinical Trial? N

Funding

Funding - Grants/Contracts

Funding - Fellowships

Gift Funding

Name of Donor : OneSight
Name of Donor : CLSA
Name of Donor : Charities Aid Foundation

Dept. Funding

Other Funding

Expedited Form

A protocol must be no more than minimal risk (i.e., "not greater than those ordinarily encountered in

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daily life') AND must only involve human subjects in one or more of the following paragraphs.

Select one or more of the following paragraphs:

1. N **Clinical studies of drugs and medical devices only when condition (a) or (b) is met.**
 - a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - b) Research on medical devices for which
 - i) an investigational device exemption application (21 CFR Part 812) is not required; or
 - ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. N **Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:**
 - a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
 - b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
3. N **Prospective collection of biological specimens for research purposes by non invasive means.**
4. Y **Collection of data through non invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)**
Examples:
 - a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
 - b) weighing or testing sensory acuity;
 - c) magnetic resonance imaging;
 - d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
 - e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
5. N **Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this paragraph may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)**
6. N **Collection of data from voice, video, digital, or image recordings made for research purposes.**
7. Y **Research on individual or group characteristics or behavior(including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or**

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quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Resources :

a) Qualified staff.

Please state and justify the number and qualifications of your study staff.

Our research team has been conducting institutional and household surveys in rural China for over 30 years. All senior study staff have doctoral degrees in economics and are fluent in the language and culture of the study areas. They have years of experience designing and implementing surveys in rural China. All team members are versed in the local language and culture.

The Stanford PI is Dr. Scott Rozelle, PhD, who holds a doctoral degree in agricultural economics. He speaks the local language (Mandarin Chinese) fluently and has worked in rural China for over 30 years. He will use his technical, linguistic, and cultural expertise to oversee survey design, implementation, and eventually, data analysis.

The China-side PIs are Dr. Linxiu Zhang, PhD, at the Chinese Academy of Sciences and Dr. Xiaopeng Pang, PhD, at Renmin University of China. Both are trained in economics and survey methodologies, and have extensive experience conducting fieldwork in China; indeed, there is probably no social scientist in academia that has collected more primary data than Dr. Zhang. Together they have organized the interventions and evaluations of at least 30 large scale Randomized Controlled Trials over the past five years. They will supervise all aspects of survey design, implementation, and analysis inside China.

In addition to the three project PIs listed above, the project will also employ two field directors:

Yaojiang Shi, PhD, Director of Northwest Socio-economic Development Research Center, Professor School of Management, Xibei University

Renfu Luo, PhD, Associate Professor, Center for Chinese Agricultural Policy at Chinese Academy of Sciences

And one medical consultant:

Nathan Congdon, MD, MPH, Professor, Zhongshan Ophthalmic Center

Dr. Congdon is a leading expert on eye care in poor areas of rural China. He speaks fluent Chinese and has extensive experience conducting surveys and running projects related to eye health among rural Chinese. He will be acting as consultant on this project for all aspects related to eye examinations.

b) Training.

Describe the training you will provide to ensure that all persons assisting with the research are informed about the protocol and their research-related duties and functions.

Our enumerator teams will receive specialized training to ensure consistent, quality data collection, and strict adherence to the project and IRB protocols.

Eye exam teams: A team of medical professionals from Zhongshan Ophthalmic Center will oversee the training of enumerators for all medical-related project activities. Nathan Congdon and Scott Rozelle will

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lead training of the teams responsible for administering the tests of visual acuity and preparing students for the test of refractive error. Local opticians will be trained to administer the test of refractive error.

Socioeconomic survey teams: These teams will be trained by one of the project PIs to administer the three-part socioeconomic survey form at baseline and endline. The survey includes a standardized academic test; a standardized mental health test; and a personal information sheet that will collect basic demographic information.

Scott Rozelle will be in charge of training all team members on details of the IRB protocol.

c) Facilities.

Please describe and justify.

Tests and surveys of students and teachers will be conducted on-site at the primary schools.

Health education training sessions will be conducted on-site at the primary schools.

Caregiver surveys will be sent home with students and mailed back to the research team in pre-paid envelopes.

d) Sufficient time.

Explain whether you will have sufficient time to conduct and complete the research. Include how much time is required.

Month 1 Baseline surveys and vision tests will be conducted during Month 1 of the survey.

Month 2-7 Treatment period: Starting in Month 2 and running through Month 7. Students in the intervention schools who are determined to need corrective lenses will be offered corrective lenses. All students in intervention schools will participate in a health education campaign to encourage proper eye care and reduce the stigma associated with wearing eyeglasses. In the control schools, nothing will be done during months 2 to 7.

Month 8 Endline survey: All project participants will be administered the same socioeconomic surveys, cognitive tests, and non-cognitive tests that were administered at baseline. The vision testing will NOT be repeated.

e) Access to target population.

Explain and justify whether you will have access to a population that will allow recruitment of the required number of participants.

We will be working with the Provincial Departments of Education in each province, who will arrange access to the sample schools. The provincial education department officials will call county education bureau officials and direct the county officials to contact the principals of each of the 360 sample schools. The principal of each school, who has legal guardianship over the students who are in school, will coordinate with the teachers in each school to allow the students to be available for survey testing at both baseline and endline.

The education system at all levels is highly supportive of this effort, as are the local Centers for Disease Control & Prevention.

f) Access to resources if needed as a consequence of the research.

State whether you have medical or psychological resources available that participants might require as a consequence of the research when applicable. Please describe these resources.

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A team of trained medical professionals specializing in eye care will be recruited from Zhongshan Ophthalmic Center. They will be oversee all aspects of the vision testing, and will also be available to address any medical problems that may arise during the baseline survey.

All children participating in the pupil dilation part of the project will be carefully instructed as to post-dilation care, which primarily involves avoiding bright sunlight for the rest of the day. As part of the protocol, the children will be provided with chairs on which to rest during the dilation process. The survey team will be fully equipped with clean tissues for wiping eyes, bottled water for hydration, and will be trained on how to speak calmly and soothingly to children who feel nervous or uncomfortable.

g) Lead Investigator or Coordinating Institution in Multi-site Study.

Please explain (i) your role in coordinating the studies, (ii) procedures for routine communication with other sites, (iii) documentation of routine communications with other sites, (iv) planned management of communication of adverse outcomes, unexpected problems involving risk to participants or others, protocol modifications or interim findings.

1. Purpose

a) In layperson's language state the purpose of the study in 3-5 sentences.

The purpose of this study is to measure the incidence of uncorrected vision among students in rural China's primary schools, and to gather information on students', parents', and teachers' attitudes towards and understanding of imperfect vision. We also hope to measure the impact of providing these students with corrective lenses and/or health education on uptake of eyeglasses, willingness to wear eyeglasses, academic performance, and mental health.

b) State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.

Broadly speaking, we hope to better understand the role of vision in education.

By showing the effectiveness of different interventions designed to reduce the rate of uncorrected vision in China's classrooms, we will be offering new evidence on best strategies for overcoming this basic (and overlooked) health problem. This information has important implications for policymakers and educators alike.

By measuring the impact of wearing eyeglasses on school performance, we will be providing first evidence of a link between vision and academic outcomes (if one exists). This would be big news in the health and development literature, and would bring needed attention to this important problem.

c) Explain why human subjects must be used for this project. (i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific behavioral traits in humans in classroom or other environment)

The purpose of the study is to determine the impact of corrective lenses on the health, educational achievement, and mental health of children in schools.

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2. Study Procedures

- a) **Please SUMMARIZE the research procedures, screening through closeout, which the human subject will undergo. Refer to sections in the protocol attached in section 16, BUT do not copy the clinical protocol. Be clear on what is to be done for research and what is part of standard of care.**

I. Create a baseline of information

1.) Measure the extent of vision problems in China's poor rural areas by testing ALL students in all sample schools.

a.) All students will be given a basic vision acuity (VA) test using a standard eye chart. --> Students will be seated a fixed distance from the eye chart, and will be asked by a survey team member to indicate the direction in which the prongs of a letter "E" are facing.

b.) Students whose VA test shows less than perfect vision will be administered a test to measure refractive error.

--> Students will be administered 1 drop of Proparacaine 0.5% (a topical anesthetic) in each eye, followed 15 seconds later by 1 drop of 1% cyclopentolate in each eye, for pupil dilation.

Children will be instructed to shut their eyes tightly for at least 5 minutes after the drops are administered. This decreases the chance of side effects. Five minutes later, a second drop of cyclopentolate 1% is administered in each eye. (The Proparacaine need not be repeated at this time, as the anesthetic is still working.) After an additional 30 minutes, if the pupillary light reflex is still present (i.e., the pupil grows smaller when a bright torch light is shined in the eye), a second round of Proparacaine and a third round of cyclopentolate is administered.

Cyclopentolate 1% is safe, and represents standard of care for measuring refractive error, as it allows the clinician to see inside the eye. Students will be seated with their eyes closed as they wait for the drug to take effect, and a nurse will be stationed nearby to offer water, tissues, or moral support as needed.

There are no side effects or risks associated with Proparacaine 0.5% administration at these dosages.

--> Students will undergo a test for refractive error using an auto-refractor.

2.) Develop a set of indicators that will help measure the impacts of the treatment program:

- Administer all fourth and fifth graders a standardized academic test
- Administer all fourth and fifth graders a standard mental health test.
- Administer all fourth and fifth graders a basic socioeconomic survey.
- Administer all fourth and fifth grade homeroom teachers a basic survey of attitudes

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towards
and knowledge of eye health.

-Administer all parents of fourth and fifth grade students a short survey of basic demographic information and attitudes and knowledge of eye health.

II. Implement "Seeing is Learning" Program

Eyeglasses Schools:

All students in eyeglasses intervention schools who tested positive for refractive error will be visited by a local optician who will measure their prescription and make them a pair of eyeglasses.

Health Education Schools:

All students, parents, and teachers in health education schools will participate in a health training program that covers proper eye health, good eye care, and the importance of wearing eyeglasses if needed. Included in the training program will be a module aimed at eliminating the stigma associated with wearing eyeglasses.

III. Conduct an endline survey.

At the end of the academic year, we will return to all schools to administer to fourth and fifth grade students, teachers, and parents the same academic test, mental health test, and socioeconomic surveys as were administered at the baseline.

Children's VA and refractive error will NOT be retested at this time.

At this time, all students in the Control Group who tested positive for refractive error will be fitted for and offered prescription eyeglasses.

b) Explain how the above research procedures are the least risky that can be performed consistent with sound research design.

1. The basic vision test is non-invasive and involves simply reading letters off of a standard eye chart. It does not involve the use of eyedrops or bright lights. It poses no risk to the child.

2. The more comprehensive eye test will be administered only to those children whose basic test indicates a problem. These children will administered a more comprehensive test to measure refractive error using an auto-refractor. This test is standard practice for determining refractive error, and requires that the children's pupils be dilated to allow for the clinician to better examine the eye. To dilate their pupils, the children will be administered 2-3 rounds of eyedrops containing 1% cyclopentolate. No more than three drops will be dropped

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into each eye. The drops are safe, and represent the only formulation effective at reducing accommodative amplitude in young children, especially those with dark irises as in China. It is the standard for clinical and research use; other drugs such as Tropicamide are inferior for this purpose. As the drops take effect, the children will be instructed to shut their eyes tightly for at least 5 minutes after the drops are administered. This decreases the chance of side effects.

The drops themselves may cause a mild stinging, not lasting more than 1-2 seconds. To avoid this stinging, the children will also be administered 1-2 drops of Proparacaine 0.5%, a topical anesthetic. There are no side effects or risks associated with Proparacaine 0.5% administration at these dosages.

There are two normal side effects to the dilation process (not to the drug), which are:

- Blurred vision, especially at close range. This is unavoidable.
- Photophobia, which can be reduced by avoiding bright lights. The children will be indoors during the exam and will be given a dark place to sit. They will be instructed to avoid playing outside for the rest of the day.

Extreme side effects of cyclopentolate include dry mouth, flushing, dry skin, dizziness, or confusion. These side effects are described in the literature as "rare", with incidence of <0.1%.

Key to avoiding these side effects will be to follow the protocol for administration carefully to prevent overdose. We will document each drop the child receives, and the time it was given.

The survey team will be equipped with water for hydration and clean tissues to wipe eyes. In the case of children who are confused or afraid, the medical team will be trained to offer calm and soothing support, and to explain that the symptoms will pass and are not harmful.

3. Results from all testing will be recorded by the enumeration team in confidence. All data will be de-identified before it is released to other researchers besides the PIs. A number will be assigned to each student. The master code with the student names will be stored in a locked filing cabinet in Beijing, in the files of Linxiu Zhang, coPI of the project.

The master code will not be destroyed because we may want to follow up and try to determine the long run impacts of the intervention.

- c) **State if deception will be used. If so, provide the rationale and describe debriefing procedures. Since you will not be fully informing the participant in your consent process and form, complete an alteration of consent (in section 13). Submit a debriefing script (in section 16).**

Not used.

- d) **State if audio or video recording will occur. Describe what will become of the recording after use, e.g., shown at scientific meetings, erased. Describe the final disposition of the recordings.**

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N/A

- e) **Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different interventional procedure, no procedure or treatment, palliative care, other research studies).**

An alternative dilating drug to cyclopentolate is tropicamide, which has the same types of side effects as cyclopentolate, but is not as effective at reducing accommodative amplitude in young children, especially those with dark irises as in China.

An alternative to pupil dilation is the use of a high-tech imaging machine that can take a microscopic photo of each eyeball. This type of machine is prohibitively expensive and impractical for field use. It is rarely used even in developed countries like the U.S.

- f) **Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?**

It will be possible for the schools to continue providing health education, as we will be training educators and providing them with educational materials such as pamphlets and posters.

All children in the study who test positive for refractive error will be told of their prescription and offered a free pair of eyeglasses. Through our study they will be introduced to the local optician and educated about the benefits of eyeglasses, so they will be able to continue wearing glasses and updating their prescription (at cost) throughout their lives.

- g) **Study Endpoint. What are the guidelines or end points by which you can evaluate the different treatments (i.e. study drug, device, procedure) during the study? If one proves to be clearly more effective than another (or others) during the course of a study, will the study be terminated before the projected total participant population has been enrolled? When will the study end if no important differences are detected?**

The study endpoint is marked by the endline survey that will be conducted at the end of the academic year. At this time all students in control schools who tested positive for refractive error will be fitted for and offered prescription eyeglasses. Besides this one-time treatment of control students, no interventions or surveys will occur after the conclusion of the endline survey.

3. Background

- a) **Describe past experimental and/or clinical findings leading to the formulation of the study.**

Our research team has participated in a study that showed both that a large percentage of rural Chinese schoolchildren have uncorrected vision, and that fitting myopic children with glasses significantly improves their academic performance. Our interviews suggest that nothing is being done to address the problem.

In this study, we will attempt to update and duplicate the results of this earlier study, and also to build on the previous research by determining willingness to pay for and actually wear eyeglasses, both with and without health education. We also hope to learn about the role of local opticians in

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fitting
children for glasses.

b) Describe any animal experimentation and findings leading to the formulation of the study.

N/A

4. Radioisotopes or Radiation Machines

- a) List all standard of care procedures using ionizing radiation (radiation dose received by a subject that is considered part of their normal medical care). List all research procedures using ionizing radiation (procedures performed due to participation in this study that is not considered part of their normal medical care). List each potential procedure in the sequence that it would normally occur during the entire study. More Info

| Identify Week/Month of study | Name of Exam | Identify if SOC or Research |
|------------------------------|--------------|-----------------------------|
|------------------------------|--------------|-----------------------------|

- b) For research radioisotope projects, provide the following radiation-related information:

Identify the radionuclide(s) and chemical form(s).

For the typical subject, provide the total number of times the radioisotope and activity will be administered (mCi) and the route of administration.

If not FDA approved provide dosimetry information and reference the source documents (package insert, MIRD calculation, peer reviewed literature).

- c) For research radiation machine projects, provide the following diagnostic procedures:

For well-established radiographic procedures describe the exam.

For the typical subject, identify the total number of times each will be performed on a single research subject.

For each radiographic procedure, provide the setup and technique sufficient to permit research subject dose modeling. The chief technologist can usually provide this information.

For radiographic procedures not well-established, provide FDA status of the machine, and information sufficient to permit research subject dose modeling.

- d) For research radiation machine projects, provide the following therapeutic procedures:

For a well-established therapeutic procedure, identify the area treated, dose per fraction and number of fractions. State whether the therapeutic procedure is being performed as a normal part of clinical management for the research participants' medical condition or whether it is being performed because the research participant is participating in this project.

For a therapeutic procedure that is not well-established, provide FDA status of the machine, basis for dosimetry, area treated, dose per fraction and number of fractions.

5. Devices

- a) Please list in the table below all Investigational Devices (including Commercial Devices used off-label) to be used on participants

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b) Please list in the table below all IDE Exempt Devices (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices) to be used on participants.

6. Drugs, Reagents, or Chemicals

a) Please list in the table below all investigational drugs, reagents or chemicals to be administered to participants.

b) Please list in the table below all commercial drugs, reagents or chemicals to be administered to participants.

6.1 Drug Name : 1% cyclopentolate

Source (i.e. Pharmacy, Sponsor, etc.) :

If not pre-mixed, where will the material be mixed and by whom:

Manufacturer :

IND# (if available) :

Dosage : 2-3 drops per eye

Administration Route:

IND Exemption

- N** Is this new and different uses of this commercially available drug, reagent or chemical?
- Y** Are all of these IND Statements true?

Investigational New Drug (IND) Regulations

The IND Regulations [21 CFR 312.2(b)] state that clinical investigation of a drug product is exempt from the requirements for an IND if all of the following apply:

- The Drug used in the investigations is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA in support of new indication for use or to support any other significant change in the labeling for the drug.
- The investigation is not intended to support a significant change in the advertising of the product.
- The investigation does not involve a route of administration or dosage level, use in a participant population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50].
- The investigation is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR part 312.7], e.g., the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold.

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6.2 Drug Name : Proparacaine 0.5%

Source (i.e. Pharmacy, Sponsor, etc.) :

If not pre-mixed, where will the material be mixed and by whom:

Manufacturer :

IND# (if available) :

Dosage : 1-2 drops per eye

Administration Route:

Dropped into eye.

IND Exemption

- N Is this new and different uses of this commercially available drug, reagent or chemical?
- Y Are all of these IND Statements true?

Investigational New Drug (IND) Regulations

The IND Regulations [21 CFR 312.2(b)] state that clinical investigation of a drug product is exempt from the requirements for an IND if all of the following apply:

- The Drug used in the investigations is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA in support of new indication for use or to support any other significant change in the labeling for the drug.
- The investigation is not intended to support a significant change in the advertising of the product.
- The investigation does not involve a route of administration or dosage level, use in a participant population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50].
- The investigation is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR part 312.7], e.g., the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold.

7. Medical Equipment for Human Subjects and Laboratory Animals

If medical equipment used for human patients/participants is also used on animals, describe such equipment and disinfection procedures.

N/A

8. Participant Population

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- a) **State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii) the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons for using such participants.**

(i) None.

(ii) The number of students included in the study is 108,000. The study will be conducted in 360 schools in 3 provinces in China's northwest region. All students in each school will be enrolled in the study - an average of 300 students from each school. (360 x 300 = 108,000) The caregivers and educators of these students will also be enrolled in the health education portion of the study, although they will not be administered any tests. We estimate that an average of one caregiver / educator will per student will participate in the health training, for a maximum of 108,000 adults. (In reality this number will be less, since not all schools will receive the health training intervention.)

(iii) Participants will be rural Chinese primary school students. These students represent all rural Chinese primary school students who may be negatively affected by uncorrected vision and whose related educational abilities and performance we are interested in studying. Some participants will be the caregivers (parents / grandparents) and educators (school teachers / principals) of the sample students. They will be chosen because of their relationship to the student and influential role in their health behaviors.

- b) **State the age range, gender, and ethnic background of the participant population being recruited.**

Male and female fourth and fifth grade elementary school students, ranging between ages 8 and 12, attending public elementary schools in rural areas of northwestern China will be recruited by randomized selection at the school level. Approximately half will be male and half will be female. Nearly all will be Han Chinese. There may be a small percentage of participants who identify as belonging to one of China's ethnic groups.

- c) **State the number and rationale for involvement of potentially vulnerable subjects in the study (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students). Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects and the additional safeguards that have been included in the protocol to protect their rights and welfare.**

Approximately 108,000 primary school students will be involved in this study. They are selected because they are representative of the target population in which we are looking to understand health and educational impacts.

In order to minimize risks, precautionary measures will include:

a) Communication between study collaborators and the local Dept. of Education/school principals (to obtain consent) and with students (to obtain assent). [as specified by Stanford University Research Compliance Office (GUI-C41 45 CFR 46.116 [OHRP] General Requirements for Informed Consent)];

b) Cooperation with Zhongshan Ophthalmic Center to ensure that trained medical professionals are on call in case of any unusual reactions to the eye exams.

c) A dark, comfortable place to sit will be provided to all students participating in the pupil dilation portion of the test for refraction error.

d) An ample supply of water for hydration and tissues to wipe eyes will be provided to all students participating in the pupil dilation portion of the test for refraction error.

- d) **If women, minorities, or children are not included, a clear compelling rationale must be provided (e.g., disease does not occur in children, drug or device would interfere with normal growth and development, etc.).**

N/A

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- e) **State the number, if any, of participants who are laboratory personnel, employees, and/or students. They should render the same written informed consent. If payment is allowed, they should also receive it. Please see Stanford University policy.**

None of the study participants will be Stanford laboratory personnel, employees, or students.

- f) **State the number, if any, of participants who are healthy volunteers. Provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which participants may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to the volunteers and the additional safeguards that have been included in the protocol to protect their rights and welfare.**

N/A

- g) **How will you identify participants for recruitment? (E.g., by: chart review; referral from treating physician; response to ad). Attach recruitment materials in Section #16 (Attachments). All Final or revised recruitment materials, flyers, etc. must be submitted to the IRB for review and approval before use. You may not contact potential participants prior to IRB approval. See Advertisements: Appropriate Language for Recruitment Material.**

We will be working with the Provincial Departments of Education in each study region. From an independent statistical source, we will identify and randomly select nationally designated poverty counties in each province. The bureau of education in each of the counties will provide us with a comprehensive list of all elementary schools. From this comprehensive list we will randomly choose our sample schools. All students in each of these schools who agree to participate in the study will be enrolled as study participants.

Once these schools are identified, the provincial department of education will arrange access to the sample schools. The provincial officials will call county bureau of education officials who will contact the 360 principals in each of the 360 sample schools. The principal of each school will coordinate with the teachers in each school to allow the students to be available for the assent discussion; baseline testing; and, in the subset of schools randomly selected as the treatment group, to begin the interventions.

Student caregivers in the health education arm of the study will be invited to the school for the health education training sessions. The school principal and the homeroom teachers will tell children to tell their parents, send letters home with the students, and also make a reminder phone call to inform parents of the time and date of the meeting. These methods are standard practice in Chinese primary schools.

- h) **Inclusion and Exclusion Criteria.**

Identify inclusion criteria.

Schools are randomly selected from areas in rural China known only to be relatively poor. All students in these schools who agree to participate in the study will be enrolled as study participants.

Identify exclusion criteria.

We are not including rich, urban areas in the randomized selection. These areas are not known to have major health problems.

- i) **Describe your screening procedures, including how qualifying laboratory values will be obtained. If you are collecting personal health information prior to enrollment (e.g., telephone screening), please request a waiver of authorization for recruitment (in section 15).**

We are not conducting screening. We are randomly selecting schools, and automatically enrolling all students in those schools. We are using no prior information at the individual level.

- j) **Describe how you will be cognizant of other protocols in which participants might be enrolled. Please explain if participants will be enrolled in more than one study.**

These students are in schools. Participants will not be involved in any other study.

- k) **Payment/reimbursement. Explain the amount and schedule of payment or reimbursement, if any, that will be paid for participation in the study. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of participants and that they do not constitute undue**

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pressure on participants to volunteer for the research study. Include provisions for prorating payment. See payment considerations

Participants will not be paid for participation. School principals will receive 100 RMB for their time and cooperation.

l) Costs. Please explain any costs that will be charged to the participant.

In one subset of schools children will be told of their eyeglasses prescription and will be offered the chance to purchase a pair of eyeglasses at a subsidized price - 50% off market price. This will be done to measure their willingness to pay for eyeglasses. At the end of the project, those children whose families chose to purchase the eyeglasses will be reimbursed for the full amount of their purchase, and children whose families chose not to purchase the eyeglasses will be offered a pair free of charge.

m) Estimate the probable duration of the entire study. Also estimate the total time per participant for: (i) screening of participant; (ii) active participation in study; (iii) analysis of participant data.

The entire intervention will last approximately 8 months, from the baseline survey in October to the evaluation survey in late May / early June. Data cleaning and analysis will continue for 6 months after the completion of the evaluation survey. Therefore, the entire study will last approximately 14 months.

(i) The visual acuity tests will take approximately 45 minutes total: 5 minutes for the basic vision test, and 40 minutes for the dilation and auto-refraction test. Only those students whose basic vision test indicates a problem will continue on to the auto-refraction test.

(ii) Active participation in the study will take approximately 2.5 hours at baseline (including the visual acuity tests described above under screening); approximately 30 minutes for children who require fitting for eyeglasses; a maximum of 2 hours for children participating in the health education intervention; and approximately 100 minutes during the endline survey (standardized academic test, mental health test, and socioeconomic survey).

(iii) 6 months, at conclusion of study

9. Risks

- a) For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk, a statement to this effect should be included. (In describing these risks in the consent form to the participant it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.)

Investigational devices.

N/A

Investigational drugs. Information about risks can often be found in the Investigator's brochure.

N/A

Commercially available drugs, reagents or chemicals. Information about risks can often be found in the package insert.

To dilate their pupils, the children will be administered 2-3 rounds of eyedrops containing 1% cyclopentolate.

The drops themselves may cause a mild stinging, not lasting more than 1-2 seconds. To avoid this stinging, the children will also be administered 1-2 drops of Proparacaine 0.5%, a topical anesthetic. There are no side effects or risks associated with Proparacaine 0.5% administration at these dosages.

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There are two normal side effects to the dilation process (not to the drug), which are:

- Blurred vision, especially at close range. This is unavoidable.
- Photophobia, which can be reduced by avoiding bright lights. The children will be indoors during the exam and will be given a dark place to sit. They will be instructed to avoid playing outside for the rest of the day.

Extreme side effects of cyclopentolate include dry mouth, flushing, dry skin, dizziness, or confusion. These side effects are described in the literature as "rare", with incidence of <0.1%.

Key to avoiding these side effects will be to follow the protocol for administration carefully to prevent overdose. We will document each drop the child receives, and the time it was given.

The survey team will be equipped with water for hydration and clean tissues to wipe eyes. In the case of children who are confused or afraid, the medical team will be trained to offer calm and soothing support, and to explain that the symptoms will pass and are not harmful.

Procedures to be performed. Include all investigational, non-investigational and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

There are two normal side effects to the pupil dilation process (not to the drug), which are:

- Blurred vision, especially at close range. This is unavoidable.
- Photophobia, which can be reduced by avoiding bright lights. The children will be indoors during the exam and will be given a dark place to sit. They will be instructed to avoid playing outside for the rest of the day.

Radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy) and associated risks.

N/A

Physical well-being.

Minimal risk.

Pupil dilation is safe. Some children may feel some mild discomfort or disorientation, but these typically symptoms pass within a few minutes. Members of the survey team will be on hand to offer calm support and assurance that the symptoms will pass and are not harmful.

Less than 1 in 1000 children may experience more severe symptoms (dizziness, flushing, dry mouth, dry skin), but these symptoms also pass within a few minutes, and the medical team will be trained to offer hydration and support.

Psychological well-being.

Students found to have refractive error will be offered education about the condition and offered treatment.

Some students who begin wearing eyeglasses for the first time may feel shy or embarrassed. There is even a chance that other students, or even less-educated adults, may tease them.

As part of our project we will be running an anti-stigma campaign in schools to discourage teasing and convince both children and adults that wearing glasses is nothing to be embarrassed about.

Economic well-being.

No risk.

Social well-being.

No risk. All survey and cognitive test results will be kept confidential from student peers and from school officials. Although names will be on the original tests, as soon as the surveys are collected, all names will be

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eliminated from the survey forms and the confidential list of names and codes will be kept in a locked filing cabinet in Beijing (with Dr. Linxiu Zhang).

Overall evaluation of Risk.

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

- b) If you are conducting international research, describe the qualifications/preparations that enable you to both estimate and minimize risks to participants. Also complete the 'http://humansubjects.stanford.edu/research/documents/intl_rschn_APP-11.doc' International Research Form and attach it in the Attachments section. If not applicable, enter N/A.**

We will be collaborating with medical experts from Zhongshan Ophthalmic Center, who will be overseeing the survey teams and all tests of visual acuity and refractive error. They will conduct the training of the survey teams, and designing safe protocol which will include sterile equipment, avoiding contact between students' eyes and the eye dropper, and every routine medical precaution for children.

- c) Describe the planned procedures for protecting against and minimizing all potential risks. Include the means for monitoring to detect hazards to the participant (and/or to a potential fetus if applicable). Include steps to minimize risks to the confidentiality of identifiable information.**

The children will be offered a dark place to sit during the pupil dilation process in order to minimize the risk of photophobia. They will be instructed to avoid playing outside for the rest of the day.

Extreme side effects of cyclopentolate include dry mouth, flushing, dry skin, dizziness, or confusion. These side effects are described in the literature as "rare", with incidence of <0.1%. Key to avoiding these side effects will be to follow the protocol for administration carefully to prevent overdose. We will document each drop the child receives, and the time it was given.

The survey team will be equipped with water for hydration and clean tissues to wipe eyes. In the case of children who are uncomfortable or disoriented, the medical team will be trained to offer calm and soothing support, and to explain that the symptoms will pass and are not harmful.

We will be collaborating with medical experts from Zhongshan Ophthalmic Center, who will be overseeing the survey teams and all tests of visual acuity and refractive error. They will conduct the training of the survey teams, and design safe protocol which will include sterile equipment, avoiding contact between students' eyes and the eye dropper, and every routine medical precaution for children.

Results from all testing will be recorded by the enumeration team in confidence. All data will be de-identified before it is released to other researchers besides the PIs. A number will be assigned to each student. The master code with the student names will be stored in a locked filing cabinet in Beijing, in the office of Linxiu Zhang, coPI of the project.

The master code will not be destroyed because we may want to follow up and try to determine the long run impacts of the intervention.

- d) Explain the point at which the experiment will terminate. If appropriate, include the standards for the termination of the participation of the individual participant Also discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.**

The project will terminate at the conclusion of the endline survey, in month 8 of the study.

As part of the assent statement, students will be told that their participation in the study is voluntary and that they can drop out at any time.

- e) Special Participant Populations**

Children's Findings OHRP. As children are involved in your research, please select one or more regulatory categories (46.404 through 46.407) below that your research falls under and provide the necessary rationale for each determination. See full regulation citation.

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- Y** 46.404 Research not involving greater than minimal risk. The research must present no greater than minimal risk to children and adequate provisions must be made for soliciting the assent of the children and the permission of their parents or guardians. Please provide rationale for the above statement.

Rationale for category selected above

1. The basic vision test is non-invasive and involves simply reading letters off of a standard eye chart. It does not involve the use of eyedrops or bright lights. It poses no risk to the child. 2. The more comprehensive eye test will be administered only to those children whose basic test indicates a problem. These children will administered a more comprehensive test to measure refractive error using an auto-refractor. This test is standard practice for determining refractive error, and requires that the children's pupils be dilated to allow for the clinician to better examine the eye. To dilate their pupils, the children will be administered 1 drop of Proparacaine 0.5% (a topical anesthetic) in each eye, followed 15 seconds later by 1 drop of 1% cyclopentolate in each eye, for pupil dilation. Children will be instructed to shut their eyes tightly for at least 5 minutes after the drops are administered. This decreases the chance of side effects. Five minutes later, a second drop of cyclopentolate 1% is administered in each eye. (The Proparacaine need not be repeated at this time, as the anesthetic is still working.) After an additional 30 minutes, if the pupillary light reflex is still present (i.e., the pupil pigns smaller when a bright torch light is shined in the eye), a second round of Proparacaine and a third round of cyclopentolate is administered. Cyclopentolate 1% is safe, and represent the only formulation effective at reducing accommodative amplitude in young children, especially those with dark irises as in China. It is the standard for clinical and research use; other drugs such as Tropicamide are inferior for this purpose. There are no side effects or risks associated with Proparacaine 0.5% administration at these dosages. Students will be seated with their eyes closed as they wait for the drug to take effect, since this reduces the likelihood of side effects, and a survey team member will be stationed nearby to offer water, tissues, or moral support as needed. There are two normal side effects to the dilation process (not to the drug), which are: - Blurred vision, especially at close range. This is unavoidable. - Photophobia, which can be reduced by avoiding bright lights. The children will be indoors during the exam and will be given a dark place to sit. They will be instructed to avoid playing outside for the rest of the day. Extreme side effects of cyclopentolate include dry mouth, flushing, dry skin, dizziness, or confusion. These side effects are described in the literature as "rare", with incidence of <0.1%. Key to avoiding these side effects will be to follow the protocol for administration carefully to prevent overdose. We will document each drop the child receives, and the time it was given. The survey team will be equipped with water for hydration and clean tissues to wipe eyes. In the case of children who are uncomfortable or disoriented, the medical team will be trained to offer calm and soothing support, and to explain that the symptoms will pass and are not harmful. 3. All medical procedures will be conducted for the sole purpose of improving the child's health via proven screening methods. All children found to have refractive error will be offered corrective lenses free of charge, either immediately, or at the end of 8 months. Conclusion: Risks are minimized; benefits are maximized. Benefits, in large part, go to the subpopulation which bears the minimal risk.

Children's Findings FDA. As your research includes children and an investigational drug/device or a commercial device is being studied, please select one or more regulatory categories (50.51 through 50.54) below that your research falls under and provide the necessary rationale for each determination. See full regulation citation.

Rationale for category selected above

10. Benefits

- a) Describe the potential benefit(s) to be gained by the participants or by the acquisition of important knowledge which may benefit future participants, etc.

This study is expected to benefit all students receiving treatment. At the same time, the

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results of the study will describe a potential causality between correcting students' vision and improved educational performance. This finding will be best extrapolated to children of the same age range being tested. Our study's benefits are concentrated among the students participating in our research.

11. Privacy and Confidentiality

Privacy Protections

- a) **Describe how the conditions under which interactions will occur are adequate to protect the privacy interests of participants (e.g., privacy of physical setting for interviews or data collection, protections for follow-up interactions such as telephone, email and mail communications).**

Confidentiality Protections: Vision tests will be done away from other students. All test results will be recorded in private and not shared with other students.

The information from the vision tests will be entered on a form with the student's name and survey id number. As soon as the data get back to Beijing, a copy will be put into a locked filing cabinet in the Chinese Academy of Sciences (in the office of Linxiu Zhang). The names will then be deleted from all electronic files.

Principal consent will be obtained privately in the principal's office. He will have the opportunity to ask questions and give his consent away from others at the school.

Confidentiality Protections

- b) **Specify PHI (Protected Health Information). PHI is health information linked to HIPAA identifiers (see above). List BOTH health information AND HIPAA identifiers. If you are using STRIDE, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol. Be consistent with information entered in section 15a.**

We will obtain individually identifiable vision test results (including results of eye chart test and lens prescriptions for children with myopia) and academic/mental health test data. However, we will not disclose individually identifiable data to other researchers. We will not disclose the real names in any published findings. The information from the vision test and scores from the academic/mental health test will be entered on a form with the student's name and survey id number. As soon as the data get back to Beijing, a copy will be put into a locked filing cabinet in the Chinese Academy of Sciences (in the office of Linxiu Zhang). The names will then be deleted from all electronic files.

- c) **You are required to comply with University Policy that states that ALL electronic devices: computers (laptops and desktops; OFFICE or HOME); smart phones; tablets; external hard disks, USB drives, etc. that may hold identifiable participant data will be password protected, backed up, and encrypted. See <http://med.stanford.edu/datasecurity/> for more information on the Data Security Policy and links to encrypt your devices.**

Provide any additional information on ALL data security measures you are taking. You must use secure databases such as RedCap <https://clinicalinformatics.stanford.edu/services/redcap.html>. If you are unsure of the security of the system, check with your Department IT representative. Please see <http://med.stanford.edu/irt/security/> for more information on IRT Information Security Services and http://www.stanford.edu/group/security/securecomputing/mobile_devices.html for more information for securing mobile computing devices. Additionally, any PHI data on paper must be secured in an locked environment.

By checking this box, You affirm the aforementioned. Y

Data (with the names deleted) will be kept on i.) a laptop computer, ii.) password protected.

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iii.) accessible only by the research team leaders. Data will be shared with the research team members only after the names have been removed. All accessible versions of the data will have names removed.

- d) Describe how data or specimens will be labeled (e.g. name, medical record number, study number, linked coding system) or de-identified. If you are de-identifying data or specimens, who will be responsible for the de-identification? If x-rays or other digital images are used, explain how and by whom the images will be de-identified.**

The data will be coded by school. The students will be randomly assigned id numbers and their names will be removed. Linxiu Zhang in Beijing will remove the identifying names.

- e) Indicate who will have access to the data or specimens (e.g., research team, sponsors, consultants) and describe levels of access control (e.g., restricted access for certain persons or groups, access to linked data or specimens).**

The research team will have access to the data. However, the access will not include that of the names of the individual participants.

- f) If data or specimens will be coded, describe the method in which they will be coded so that study participants' identities cannot be readily ascertained from the code.**

The data will be coded by school. The students will be randomly assigned id numbers and their names will be removed. Linxiu Zhang in Beijing will remove the identifying names.

- g) If data or specimens will be coded, indicate who will maintain the key to the code and describe how it will be protected against unauthorized access.**

The key to the code will be kept in locked filing cabinet in the Chinese Academy of Sciences, Beijing (in the office of Linxiu Zhang). The names will be deleted from all electronic files and all hard copies of the survey forms.

- h) If you will be sharing data with others, describe how data will be transferred (e.g., courier, mail) or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, describe how you will secure the data while in transit. See <http://www.stanford.edu/group/security/securecomputing/>. Additionally, if you will be using or sharing PHI see <https://uit.stanford.edu/security/hipaa> <https://uit.stanford.edu/security/hipaa>.**

A dataset for the entire research team (and for electronic transmission) will be developed with student names removed to protect identities. Since there will not be names on any files that will be transmitted, the information will be secure in transit.

- i) How will you educate research staff to ensure they take appropriate measures to protect the privacy of participants and the confidentiality of data or specimens collected (e.g. conscious of oral and written communications, conducting insurance billing, and maintaining paper and electronic data)?**

Research team members and related staff will be trained in the testing and survey protocol to record responses/observations out of view from others; shield records from others; not to discuss the performance of individuals on tests while in the presence of others.

We will have official training sessions before the commencement of the project. The two PIs, Zhang from Chinese Academy of Sciences, and Rozelle from Stanford University, will train BOTH the team supervisors and survey teams.

During the survey, team leaders will maintain the aggregated data files on a password protected computer. When all data are entered they will be removed from all machines except for the machine of Prof. Zhang at the Chinese Academy of Science. This file will be password

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protected. A dataset for the entire research team (and for electronic transmission) will be developed with student names removed to protect identities.

12. Potential Conflict of Interest

Investigators are required to disclose any financial interests that reasonably appear to be related to this protocol.

You will be unable to submit this protocol until all financial interest tasks are completed. "javascript:void(0);" onClick="javascript:startResendOpacs();return false;" Click here to send reminder emails.

Financial Interest Tasks

| Investigators | Role | Email | Has Financial Interest? | Date Financial Interest Answered | Date OPACS Disclosure Submitted | Date OPACS Review Completed |
|-----------------|------|----------------------|-------------------------|----------------------------------|---------------------------------|-----------------------------|
| Scott D Rozelle | PD | rozelle@stanford.edu | N | 06/02/2016 | N/A | N/A |

13. Consent Background

13.1 Waiver of Documentation Principal Consent Form

Sponsor's Consent Version Number: (if any) :

- a) Describe the informed consent process. Include the following.
 - i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)
 - ii) When and where will consent be obtained?
 - iii) How much time will be devoted to consent discussion?
 - iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?
 - v) What steps are you taking to minimize the possibility of coercion and undue influence?
 - vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

(i) Trained members of the field survey team will be obtaining consent. All will be trained in the details of the consent process, and will be extremely familiar with the intervention itself. (ii) Consent will be obtained in the principal's office before the start of the program. (iii) Fifteen minutes will be devoted to consent discussion, including ten minutes to describe the study, and five minutes to ask questions. (iv) Yes. (v) The members of the research team responsible for obtaining consent will be fully trained in the consent process. Principals will be notified that participation in the study is voluntary. (vi) N/A

- b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See /hrpp/Chapter12.html#ch12_2 HRPP Chapter12.2 for guidance.

The information will be conveyed to principals orally, according to a predetermined script in Chinese. (The English translation of this script is appended to this protocol application.) Principals will be asked if they understand what will be required of them.

- c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how

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you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

All school principals, by the very nature of their position of authority within the school, can be considered competent to participate in the decision-making process. We will ensure that they are provided with sufficient information to make an informed decision.

Select one of the following regulatory criteria for a waiver of documentation (signature) and provide a protocol-specific justification:

- 1) **45 CFR 46.117(c)(1). For research that is not subject to FDA regulation, the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.**
- 2) Y **45 CFR 46.117(c)(2). For research that is not subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**
- 2) **21 CFR 56.109(c)(1). For research that is subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**

Rationale for above selection:

The principals' involvement in the study is minimal and mainly involves granting researchers access to student participants.

13.2 Waiver of Documentation Educator Consent Form

Sponsor's Consent Version Number: (if any) :

- a) **Describe the informed consent process. Include the following.**
 - i) **Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)**
 - ii) **When and where will consent be obtained?**
 - iii) **How much time will be devoted to consent discussion?**
 - iv) **Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?**
 - v) **What steps are you taking to minimize the possibility of coercion and undue influence?**
 - vi) **If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.**

(i) Trained members of the field survey team will be obtaining consent. All will be trained in the details of the consent process, and will be extremely familiar with the intervention itself. (ii) Consent will be obtained privately outside of the classroom before the start of the program. (iii) Ten minutes will be devoted to consent discussion, including five minutes to describe the study, and five minutes to ask questions. (iv) Yes. (v) The members of the research team responsible for obtaining consent will be fully trained in the consent process. Educators will be notified that participation in the study is voluntary. Consent will be obtained privately. (vi) N/A

- b) **What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See /hrpp/Chapter12.html#ch12_2 HRPP Chapter12.2 for guidance.**

The information will be conveyed to teachers orally, according to a predetermined script in Chinese. (The English translation of this script is appended to this protocol application.) Teachers will be asked if they understand what will be required of them.

- c) **What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.**

All school teachers, by the very nature of their position within the school, can be considered competent to participate in the decision-making process. We will ensure that they are provided with sufficient information

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to make an informed decision.

Select one of the following regulatory criteria for a waiver of documentation (signature) and provide a protocol-specific justification:

- 1) **45 CFR 46.117(c)(1). For research that is not subject to FDA regulation, the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.**
- 2) Y **45 CFR 46.117(c)(2). For research that is not subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**
- 2) **21 CFR 56.109(c)(1). For research that is subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**

Rationale for above selection:

The teachers' involvement in the study is minimal and mainly involves filling out a short survey of eye health and (in some schools) listening to a short presentation about eye health at school.

13.3 Waiver of Documentation Parental Consent Form

Sponsor's Consent Version Number: (if any) :

- a) Describe the informed consent process. Include the following.
 - i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)
 - ii) When and where will consent be obtained?
 - iii) How much time will be devoted to consent discussion?
 - iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?
 - v) What steps are you taking to minimize the possibility of coercion and undue influence?
 - vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

(i) Consent will be obtained remotely. (ii) Consent will be obtained remotely. The survey form with the consent script will be sent home with students. Parents will read the consent script and decide for themselves whether they want to fill out the survey. If they do fill it out, it will then be mailed directly to the research team in a secure, prepaid envelope. If they choose not to fill it out, they will simply not return the form. (iii) There will be no discussion - just a letter home. Parents can peruse the letter for as long as they like, and they will have the opportunity to contact the survey team at their leisure if they have any questions. (iv) Yes. (v) The parents will be able to decide privately and in the comfort of their own home whether to participate in the survey. If they choose not to participate, the only people who will know are members of the research team in Beijing. (vi) N/A

- b) **What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See /hrpp/Chapter12.html#ch12_2 HRPP Chapter12.2 for guidance.**

There is no concrete procedure to assess understanding. If the parents have questions about the consent form, they can call the research team. If they cannot read the form (either illiterate or seeing impaired), then they will simply not fill out the survey form.

- c) **What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent, (iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.**

Our survey targets literate adults who bear primary responsibility for caring for their child(ren). The child will be instructed to give the survey form (and consent document) to their primary caregiver at home. The caregiver will then have to read the consent document and survey instructions before participating in the project. By the very nature of their position as a literate, primary caregiver, they exhibit the capacity and competency to participate in the decision-making process.

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Select one of the following regulatory criteria for a waiver of documentation (signature) and provide a protocol-specific justification:

- 1) **45 CFR 46.117(c)(1). For research that is not subject to FDA regulation, the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.**
- 2) Y **45 CFR 46.117(c)(2). For research that is not subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**
- 2) **21 CFR 56.109(c)(1). For research that is subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**

Rationale for above selection:

The caregivers' involvement in the study is minimal and mainly involves filling out a basic survey form about knowledge of and attitudes towards eye health.

14. Assent Background (less than 18 years of age)

14.1 Assent

Assent Script - English - Seeing is Learning

- a) Describe the assent process. Include the following:
- (i) Who is obtaining child assent? (The person must be knowledgeable about the study.)
 - (ii) When and where will assent be obtained?
 - (iii) Will a parent or guardian be present when assent is obtained?
 - (iv) How much time will be devoted to the assent discussion?
 - (v) Will these periods provide sufficient opportunity for the child to consider whether to assent?
 - (vi) What steps are you taking to minimize the possibility of coercion and undue influence?

i) The survey enumeration team. They will be trained in IRB protocol, including the assent process, by the project PI.

ii) Assent will be obtained in the primary schools, before the testing and program participation occur.

iii) A guardian (school principal) will be present when assent is obtained.

iv) We expect the assent discussion to last 15 minutes.

v) Yes, after the 5 minute explanation of the study procedures, students will have 10 mins to ask questions and make a decision.

vi) We are making it clear to the principal, the teachers, and the students themselves that the students are free to participate or not participate. It is up to them. Neither the principals nor teachers have any incentive to force children to participate.

- b) **What is the procedure to assess the child's understanding of the information contained in the assent? How will the information be provided to the child if he/she does not understand English or has a hearing impairment? How will affirmative assent be obtained (e.g., oral response, signature on form, combination of methods, other)?**

The field teams will converse with the children and ask questions to be sure they understand. The information will be conveyed in Mandarin by the bilingual field team members, who understand the study. We will not include hearing impaired children in the study, to avoid the risk that we are not able to effectively communicate the study to those with impaired hearing. (Special resources for the hearing impaired may not be available in these rural under-resourced schools that constitute our study sample.) Assent will be obtained orally.

- c) **What steps are you taking to determine that the child has the capacity to participate in the**

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decision-making process?

There will be no undue influence and no coercion. We are talking to the teachers and principal at each school to make clear that those students who do not wish to participate need not participate.

15. HIPAA Background

16. Attachments

| Attachment Name | Attached Date | Attached By | Submitted Date |
|-------------------------------------------|---------------|-------------|----------------|
| Student Survey Form | 07/02/2012 | amedina5 | |
| Student Cognitive Test | 07/02/2012 | amedina5 | |
| Student Mental Health Test | 07/02/2012 | amedina5 | |
| Teacher Survey Form | 07/02/2012 | amedina5 | |
| Household Survey Form | 07/02/2012 | amedina5 | |
| International Research Supplemental Quest | 07/13/2012 | monicac1 | |
| Scientific Review Form | 07/16/2012 | monicac1 | |

Obligations

The Protocol Director agrees to:

- Adhere to principles of sound scientific research designed to yield valid results
- Conduct the study according to the protocol approved by the IRB
- Be appropriately qualified to conduct the research and be trained in Human Research protection, ethical principles, regulations, policies and procedures
- Ensure all Stanford research personnel are adequately trained and supervised
- Ensure that the rights and welfare of participants are protected including privacy and confidentiality of data
- Ensure that, when de-identified materials are obtained for research purposes, no attempt will be made to re-identify them.
- Disclose to the appropriate entities any potential conflict of interest
- Report promptly any new information, modification, or unanticipated problems that raise risks to participants or others
- Apply relevant professional standards.

Any change in the research protocol must be submitted to the IRB for review prior to the implementation of such change. Any complications in participants or evidence of increase in the original estimate of risk should be reported at once to the IRB before continuing with the project. Inasmuch as the Institutional Review Board (IRB) includes faculty, staff, legal counsel, public members, and students, protocols should be written

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in language that can be understood by all Panel members. The investigators must inform the participants of any significant new knowledge obtained during the course of the research.

IRB approval of any project is for a maximum period of one year. For continuing projects and activities, it is the responsibility of the investigator(s) to resubmit the project to the IRB for review and re-approval prior to the end of the approval period. A Notice to Renew Protocol is sent to the Protocol Director 7 weeks prior to the expiration date of the protocol.

Department Chair must approve faculty and staff research that is not part of a sponsored project. VA applicants must have Division Chief or Ward Supervisor approval. E-mail the Department Chair approval to IRBCoordinator@lists.stanford.edu.

All data including signed consent form documents must be retained for a minimum of three years past the completion of the research. Additional requirements may be imposed by your funding agency, your department, or other entities. (Policy on Retention of and Access to Research Data, Research Policy Handbook, <http://doresearch.stanford.edu/policies/research-policy-handbook/conduct-research/retention-and-access-research-data>)

PLEASE NOTE: List all items (verbatim) that you want to be reflected in your approval letter (e.g., Amendment, Investigator's Brochure, consent form(s), advertisement, etc.) in the box below. Include number and date when appropriate.

Y By checking this box, I verify that I, as the Protocol Director (PD) responsible for this research protocol, have read and agree to abide by the above obligations, or that I have been delegated authority by the PD to certify that the PD has read and agrees to abide by the above obligations.