Spectacles for Patients with Down Syndrome

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Study Protocol as defined in the Data and Safety Monitoring Plan

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Data and Safety Monitoring Plan

For

Identification of Optimum Spectacle Prescriptions for Patients with Down Syndrome

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Summary of the protocol

• Brief description of the protocol (Study design)

The purpose of this study is to test the hypothesis that metric-derived spectacle prescriptions based on wavefront aberration measurements of the eyes of individuals with Down syndrome can provide an improvement in visual acuity over that obtained with spectacle prescriptions based on standard clinical prescribing techniques. Aim 1 is designed to collect wavefront aberration measurements from a sample of 30 individuals with Down syndrome to refine the process of determining metric-derived spectacle prescriptions from wavefront data. Up to 30 control subjects without Down syndrome will validate the algorithm to identify metric-derived corrections by performing visual acuity measures while viewing projected acuity charts simulating the retinal image quality of participants with Down syndrome. Aim 2 consists of a phase II clinical trial to test this hypothesis by dispensing spectacle prescriptions (1 clinically derived and 2 metric-derived) to participants with Down syndrome in random order for 2 months each. Aim 3 will assess the ability to predict on-eye visual acuity performance of individuals with Down syndrome wearing metric-derived spectacles by comparing visual acuity measures obtained from 5 control observers without Down syndrome viewing charts simulating retinal image quality of individuals with Down syndrome to actual acuity measures obtained from participants with Down syndrome during Aim 2. In addition to these 3 aims, a pilot study will be included to validate the use of a temperature sensor data logger to monitor spectacle wear time, a device that will be utilized during the Aim 2 clinical trial. This DSM Plan is written in reference to Aim 2.

A clinical examiner (who will later serve as the masked examiner) will first perform a complete eye examination on participants with Down syndrome to include presenting distance and near visual acuity, measures of binocular function (depth perception, eye alignment), and pupil size measurements with an infrared camera in both normal and dim room illumination. The examiner will use any clinical techniques indicated to determine what she believes to be the best clinical refraction for each individual participant. This may include the prescription of a bifocal, given evidence that the majority of individuals with DS do not have adequate accommodation (Anderson, 2011; Cregg, 2001; Woodhouse, 1993) and may benefit from bifocal prescriptions (Nandakumar, 2010; Stewart, 2005). Participants will then select frames for their new spectacle prescriptions from the University Optical Services. Throughout the examination, the parent/guardian of each participant will complete the Vineland Behavioral Assessment survey about the participant's adaptive abilities. In the case of participants who have self-consented due to the lack of a parent/legal guardian (e.g. the individual is their own legal representative), the participant will be asked to identify an individual who knows them well and interacts with them on a routine basis, preferably a family member, to attend a study visit to complete the survey. This survey will be scored by study personnel to assign an adapted age to the patient as an indication of their developmental ability. Data will later be analyzed with this adapted age as a predictor variable to identify associations between acuity improvement and developmental ability.

After completion of the examination, an unmasked study investigator will perform a minimum of three repeated, dilated wavefront measurements with the Discovery System. From these measures, calculations of image quality metrics will be performed within 1 week following the eye examination using the methodology defined previously from the work conducted in Aim 1. From this analysis, two alternative metric-derived prescriptions will be selected. For a metric-derived prescription to be considered, it must increase retinal image quality (as determined by comparison of computed metric values to the clinically-derived correction), and it must differ from the clinically determined prescription by an amount greater than the ANSI Z80.1 standards for prescription spectacle verification.

Three identical spectacle frames will be ordered, and each filled with a different prescription: 1) clinically derived, 2) metric-derived #1, and 3) metric-derived #2. If a bifocal was prescribed for the clinically derived prescription, the same add power will be included for each of the metric-derived corrections to maintain an equal shift in the image plane for near viewing with each prescription. Participants will return for a dispensing visit when the spectacles are ready.

At the initial dispensing visit, an unmasked examiner will verify the power of each pair of spectacles and label them according to the randomization order for dispensing. A masked examiner will then perform both distance and near visual acuity, as well as binocularity testing (cover test and near stereoacuity) for each of the three pairs of spectacles. These values will be compared to the presenting measures from the initial eye examination as a precaution to ensure that participants are not dispensed spectacles that provide worse visual function than they had when presenting to the study. Any experimental prescription which causes visual acuity to degrade more than 1 line from presenting acuity at either distance or near, depth perception to decrease more than 2 levels from presenting, or results in the manifestation of an eye-turn that was previously not observed, will not be dispensed to the patient. All remaining prescriptions (up to 3) will be dispensed to the participant one at a time in random order for two month wearing intervals with a SmartButton data logger placed in a mount on the temple of the spectacles. The data logger will provide an objective assessment of spectacle wear time for each prescription. The decision to select a two month wear interval was based on clinical experience related to patient adaptation time to new spectacle corrections, scientific evidence for perceptual adaptation time to previously uncorrected astigmatic refractive error (Vinas, 2012), and a desire to allow adequate time for assessment of the wearing profile of each individual. Although each prescription will be dispensed for two months, participants will be asked to return at one-month intervals to perform adapted visual acuity measures, download data logger readings, and complete a brief survey regarding their opinion of the spectacles. Monitoring patients at monthly intervals will allow us to evaluate the cumulative effects of spectacle correction on visual acuity and identify any treatment order effects.

After completion of all spectacle prescription dispensing periods, the clinical examiner will be unmasked and determine, through evaluation of acuity results and consultation with the patient and their parent/guardian, which pair of spectacles is recommended for continued wear. Participants will be asked to return for one additional follow-up after 6 months additional wear of the recommended prescription. At the follow-up visit, visual acuity and binocularity will be measured to determine whether additional improvements occur with continued spectacle wear.

- ## Primary and secondary outcome measures

The primary outcome measure is:
Adapted visual acuity - compared after two months wear time for each pair of spectacles. Visual acuity will be measured monocularly by a masked clinical examiner using custom chart presentation software in which participants read a series of three charts from 100% seeing until 5 letters are missed. The average acuity of the three charts will be recorded for each eye. ETDRS charts will be attempted first with HOTV charts reserved as an alternate for participants who are unable to reliably perform ETDRS due to cognitive limitations.

Secondary outcome measures include:
1) Initial visual acuity – obtained by a masked examiner at the initial dispensing visit for all three spectacle prescriptions. Acuity will be obtained in the manner described above prior to any adaptation time to the spectacles.

2) Spectacle wear time – obtained by a temperature sensor data logger attached to the temple of each pair of spectacles. Total wear time over the two month trial for each pair of spectacles will be compared with the interpretation that longer wear time is indicative of better visual performance, or conversely, short duration wear time is indicative of poorer visual performance.

3) Spectacle Assessment Survey – administered to participants after each two month wear period for each pair of spectacles. The survey consists of the following questions which will be read to the participants who will then respond by pointing to a picture of the facial expression that corresponds to their opinion (5 point frown to smile scale).

A) Do you like wearing this pair of glasses?
B) How well do you see with this pair of glasses when looking far away?
C) How well do you see with this pair of glasses when looking up close?
D) Do you see better with these glasses than without glasses?

Responses will be tallied on a scale from1 – 5 and summed for the four questions. Larger total scores will indicate greater participant preference.

4) Final participant comparison of spectacles – administered at the end of all spectacle trial periods. The patient will be asked to compare all three pairs of spectacles and indicate which they prefer.

- ## Inclusion/exclusion criteria

Inclusion critera:
Participants must be 18 years of age or older and have a diagnosis of Down syndrome.

Exclusion criteria:
Participants cannot have nystagmus (estimated to be 5 to 17% of the population), visually significant media opacities (estimated to be 13% of the population), strabismic amblyopia (estimated to be 15% of the population), or anisometropic amblyopia (estimated to be 7% of the population) (Berk, 1996; da Cunha, 1996; Tsiaras, 1999). Given that these conditions often co-exist, we expect to exclude approximately 30% of potential participants with Down syndrome.

- ## Power calculation and sample size

We will enroll 30 individuals with Down syndrome for this trial which provides us the power to detect a difference as small as 1.9 letters between visual acuity measures; however, we will only consider a difference of greater than 5 letters to be clinically meaningful given the intra-observer test-retest variability of visual acuity measures (Lovie-Kitchin, 2000).

Trial Management

- ## List of participating enrolling clinics

This is a single site study with all participants enrolled at the University of Houston, College of Optometry in Houston, TX. An additional site, The Ohio State University College of Optometry, will be included for recruitment and testing for a cold weather environment to complete the pilot study (data logger development) listed below, but will not be involved in the Aim 2 study discussed in this DSM Plan.

- **Projected timetable**

This trial is Aim 2 of three aims that will be sequentially pursued over the course of the grant funding. A projected timetable is shown below.

Aims/Experiment	**9/14-8/15**	**9/15-8/16**	**9/16-8/17**	**9/17-8/18**	**9/18-8/19**
Pilot Study - Data Logger Development	X	X			
Aim 1, Exp 1.1 – Develop Metric-Derived Correction Algorithm	X	X			
Aim 1, Exp 1.2 – Identify Most Predictive Metrics for DS Eyes	X	X			
Aim 2, Exp 2.1 – Treatment Trial Part 1: Initial Acuity Outcome			X	X	
Aim 2, Exp 2.2 – Treatment Trial Part 2: Adapted Acuity Outcome			X	X	X
Aim 3, Exp 3.1 – Control Study for Exposure to Foreign Aberrations				X	
Aim 3, Exp 3.2 – Agreement between Predicted & Actual Acuity Improvement				X	X

- **Target population distribution (e.g, women, minorities, etc)**

The targeted enrollment for this trial is to have an equal number of males and females and a racial distribution representative of the population of Houston, TX in which the research will be conducted. No participants will be excluded from participation based upon gender, ethnicity, or race; however, it is not anticipated that participants of American Indian or Native Hawaiian race will be enrolled in the study simply due to the small numbers of persons from these races in the population of Houston, TX. The anticipated racial distribution of participants, based on the make-up of Houston, TX, is shown in the table below (note this only reflects anticipated enrollment for Aim 2 – the clinical trial portion of the grant). We will attempt to adhere to the targeted enrollment outlined in the included table; however, this is a small scale study investigating a special population (participants with Down syndrome) and thus we will not turn away potential participants who respond to our recruitment efforts simply because of an effort to strictly adhere to a specific balance of gender or minority groups. The purpose of this study is to investigate the use of metric-derived spectacle corrections to improve visual acuity in participants with Down syndrome. There is no evidence that the effectiveness of this treatment modality should be associated with race, ethnicity, or gender.

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiin or Other Pacific Islander	0	0	0	0	0
Black or African American	1	1	0	0	2
White	6	6	6	6	24
More than One Race	0	0	1	1	2

Total	8	8	7	7	30

Data Management and Analysis

- ## Data acquisition and transmission

Complete Eye Examination Findings:
Eye examination findings from the clinical masked examiner will be first documented on paper by the clinical examiner during the study visit. These data will subsequently be scanned and saved with the participant's unique study ID on the PI's laboratory computer. Data will also be entered by the clinical masked examiner into the University of Houston Eye Institute Electronic Medical Records system. Participant's parents/guardians, or the self-consenting participant will complete a HIPAA authorization form prior to entry of the findings in the system. The intent is to have clinical examination findings available as part of the participant's medical records for their potential future medical care outside of the study.

Visual acuity measures (primary and secondary outcomes):
Visual acuity will be performed with a custom Matlab software program in which an unmasked examiner will key in participant responses to letter charts presented on a monitor. Each visual acuity test will result in an electronic file that will be saved to the PI's laboratory computer using the participant's unique study ID.

Temperature sensor data (secondary outcome):
Temperature data indicating spectacle wear time will be recorded by a commercially available data logger mounted to the temples of the participant's spectacles. Each month, participants will return to the lab and the data will be extracted from the data logger into an excel file on the PI's laboratory computer. Data files will be saved by the participant's unique study ID and the temperature data deleted from the sensor.

Spectacle Assessment Survey:
Participant responses to the spectacle assessment survey will be first documented on paper and later scanned by unmasked study personnel and saved on the PI's laboratory computer with the participant's unique study ID.

Vineland Behavioral Assessment Survey:
The participant's parent/guardian, or other appropriate individual will complete this survey on paper during the initial examination visit. The survey score sheet will then be completed by study personnel and all documents scanned and saved on the PI's laboratory computer with the participant's unique study ID.

Any paper documents generated at study visits will be stored in the PI's secure laboratory. Electronic documents will be stored and accessed by study personnel in the PI's secure network storage folder (only lab personnel accounts have access) maintained on the University of Houston College of Optometry server. De-identified study data may be transmitted between lab personnel via email. There will be no transmission of data outside of the study team, all of whom are part of the University of Houston College of Optometry.

- **Data entry methods**

See section above (Data acquisition and transmission) regarding data entry methods.

- **Data analysis plan**

Differences in adapted visual acuity will be compared across spectacle types for all participants using dependent t-tests to identify the prescription type(s) with best-adapted performance. Differences in initial (un-adapted) acuity will also be compared across spectacle types for all participants using dependent t-tests to identify the prescription type(s) with best initial performance.

Survey scores and differences in wear-time as determined by analysis of the temperature sensor readings will be compared to identify prescription type(s) with best patient preference and wear time compliance.

Developmental ability (as ranked by the adaptive age obtained by the Vineland survey) will be used as a predictor variable for comparisons of visual acuity to identify any relationship between developmental ability and acuity performance.

Quality Assurance

- **Procedures in place to ensure the validity and integrity of the data**

The primary outcome measure is visual acuity measured on a computer monitor. Each week, the monitor brightness will be verified with a Minolta light meter and the test distance (chinrest to monitor) measured to ensure that these elements remain standardized across participants and study visits.

Prior to dispensing temperature sensor data loggers to a patient, each sensor will be placed in a location of known temperature for 4 hours to verify that the readings are accurate and do not fluctuate over time.

The masked clinical examiner will obtain the visual acuity and spectacle assessment survey data to guard against bias in the outcomes related to prescription type.

- **Procedures to guarantee the accuracy and completeness of the data, during data collection, entry, transmission, and analysis.**

All study visits will be attended by a minimum of two study personnel (one masked to spectacle assignment and one unmasked). The unmasked personnel will maintain a checklist of procedures to be performed to assure that the masked examiner completes all necessary study measures.

A co-investigator who did not attend the study visit will review all data files generated from each study visit to ensure completeness. Study findings that are documented on paper and scanned will ultimately be converted to Excel sheets for data analysis. The co-investigator will oversee this process and check the transcription of data by unmasked study personnel from paper forms to Excel files for errors. Any

errors, omissions, or suspected errors identified by the co-investigator will be returned to the unmasked study personnel for verification/reconciliation. This process should be manageable within the grant team given the small number of participants (30) enrolled in the trial. In addition, the primary outcome measure (visual acuity) is stored directly in a file generated by the acuity presentation software and requires no transcription, thus the risk of error in that study measure is very low.

The study statistician will review all de-identified data for outliers and generate reports to the PI to verify data which fall outside of the observed trends of the group. Data analysis will be a group effort between the PI, unmasked study personnel, and the statistician. All data analysis files will be stored on the PI's secure network storage folder (accessible only by study personnel) to ensure that the current files are centrally accessible and that multiple versions do not exist.

- ## Reporting of IRB actions to NEI

The PI will annually provide the NEI with documentation of human subjects' protocol approval by the University of Houston Committee for the Protection of Human Subjects. Any actions by the UH CPHS against the PI or other study personnel will be reported to the NEI via the grant program officer.

- ## Report of changes or amendments to the protocol

Changes and amendments to this protocol will be reported to the NEI via the grant program officer.

- ## Trial stopping rules

This trial is anticipated to be conducted over the course of 3 years, enrolling 30 participants for 1 year total follow-up each. Over the course of the first 6 months of the trial, all participants are expected to receive the opportunity to wear the experimental treatment (metric-derived spectacle prescriptions) – the only barrier to this being the acuity and binocularity criteria that may preclude dispensing a metric-derived prescription to a given participant (e.g. initial acuity with the metric derived prescription is too poor to dispense). Given the small size of the trial, short duration, and fact that all individuals will receive the experimental treatment if it meets the visual acuity and binocularity criteria, it is not anticipated that the trial will stop prematurely. Safeguards are already in place to 'stop the trial' for a given participant as mentioned already – metric-derived spectacles that reduced visual acuity or impair binocularity will not be dispensed and tested at all. The PI will monitor the number of spectacle prescriptions that fail to meet the performance criteria for dispensing throughout the duration of the trial. If this is found to be the case for the first 5 of 30 participants (i.e. no metric-derived prescriptions reach the threshold to be dispensed), then the trial will stop and the study team will re-evaluate the work from Aim 1 to determine whether the algorithm to identify the metric-derived spectacles is faulty. With regards to stopping the trial early due to an overwhelming benefit of the experimental treatment to the participants – given the small sample size of the study, it is not expected that such overwhelming evidence will exist prior to completion of the full sample. In addition, all participants will be given the opportunity to evaluate the experimental treatment (if it meets initial acuity and binocularity criteria) and ultimately offered to keep this treatment (if it performs best of the three prescriptions), and thus no participant will ultimately be denied the experimental treatment if it does indeed perform best for them individually.

- ## Management of conflict of interest (COI)

The data and safety monitoring of this trial will ultimately be the responsibility of the PI. Any COI, by virtue of being the PI, in data and safety monitoring will be managed by the PI reporting directly to the

IRB of record and by keeping NEI fully informed. The DSM Plan will be submitted to the IRB and any adverse events or unexpected problems will also be reported to the IRB. In addition, the DSM Plan will be submitted to the NEI program officer for approval. The final detailed DSM Plan will also be submitted via the grant signing official to NEI. The PI will also submit an annual progress report to NEI that includes a summary of any data and safety monitoring issues, especially those that may affect level of risk. The PI will also provide NEI with IRB approvals.

Trial Safety

- ## Potential risks and benefits for participants

Potential risks:
Risks of confidentiality will be minimized by maintaining the link between participant IDs and personally identifying information in the PI's locked, limited access laboratory. All other data will be de-identified and stored with a unique identifier that cannot be linked back to the participant without the link maintained by the PI.

Risks of adverse events from dilation drops will be minimized by screening the participants in advance for medical and ocular conditions which contraindicate the use of dilation drops. Common side effects of dilation drops (Tropicamide and Phenylephrine) include blurred vision, headache, sensitivity of eyes to light, and stinging of the eye when the medicine is applied. A rare side effect of dilation drops is acute increased intraocular pressure which can largely be avoided by pre-screening patients for indications of increased risk (such as slit lamp examination to identify narrow anterior chamber angles and measurement of pre-dilation intraocular pressure). Any participants who do experience adverse events from dilation drops will receive care from one of the licensed optometrists at the College of Optometry, including the potential for care from the after-hours resident on-call at no cost. Risks of discomfort and boredom when performing the study measures will be minimized by allowing participants to take frequent breaks during study measurements.

Risks of poor vision while wearing study spectacle prescriptions will be minimized by only dispensing those prescriptions which do not decrease visual acuity (greater than 1 line) or binocularity (2 level reduction in depth perception, or manifestation of new eye-turn) from the way participants presented to the study. Participants with Down syndrome are considered a vulnerable population due to their intellectual disability. These participants will be protected in that informed parental / guardian permission will be obtained first and then informed participant assent obtained. Both informed parental permission and informed participant assent will be required for enrollment in the study with the exception of individuals who do not have parents or legal guardians. In these specific cases, individuals will provide informed consent after it is determined that the participant has capacity to consent by demonstrating comprehension of the requirements of the study and the study purpose. The inclusion of participants with Down syndrome is necessary to address the problem of visual impairment in this specific population. Risks for this population are no greater than would be experienced from a routine eye examination and subsequent spectacle treatment and the findings that result from this work may lead to future treatment options that will directly benefit persons with Down syndrome.

Potential benefits:
Participants with Down syndrome will receive a complete eye examination, as well as up to three pairs of spectacles. At the conclusion of the study, participants will be permitted to keep the pair of spectacles that performed the best, as well as the frames from the other two pairs. Our hypothesis is that some of these spectacles may provide significant improvements in visual acuity over what

participants currently experience with their habitual corrections. These benefits outweigh the risks in this study, which are no different than those associated with a routine eye examination.

- **Collection and reporting of AEs and SAEs**

Adverse Events:
Given the strict criteria to dispense a pair of spectacles, anticipated adverse events are expected to be few and primarily related to eye strain from adaptation to a new spectacle prescription. To identify these AEs, parents/guardians of participants, or another appropriate individual who is in close, regular contact with the participant, will be contacted both one day and one week after each new spectacle prescription is dispensed by a clinical study examiner. During these calls, examiners will ask if the participant is having any difficulty with the prescription. If concerns are great enough to warrant a study visit, participants will be seen by the unmasked examiner to address the concerns. All AEs as a result of these phone interviews will be documented in the participant's file, along with their resolution. In addition to planned solicitation of participant difficulties with prescriptions, any unsolicited participant complaints or findings discovered at scheduled study follow-ups will be managed in the same fashion.

Serious Adverse Events:
The risk for SAEs in this study is limited and primarily related to the rare possibility for an acute increase in intraocular pressure after instillation of dilation drops during the study visit. This SAE would most likely occur in the few hours post-dilation, and thus participants and their family members will be advised to contact the investigator immediately if symptoms such as headache and nausea develop. The management of this, and other, SAEs is detailed below. All SAEs will be documented in the participant's files, along with their resolution. All SAEs will also be reported to the University of Houston Committee for the Protection of Human Subjects via their online reporting system (SAE Time Frame: 24 hours), as well as the NEI via the Program Officer.

- **Management of SAEs or other study risks**

Any SAE or other study risk will be managed by the unmasked clinical examiner, or the PI, both of whom have Clinical Licenses. If a participant needs intervention of an ocular nature when either of those individuals are unavailable, care to resolve the acute event will be provided at no-cost to the participant by the on-call doctor at the University of Houston University Eye Institute, as stated above under risks. If the adverse event is not of an ocular nature, the participant will be referred to the appropriate professional at the expense of the participant's parent/guardian/responsible party.

DSM Plan Administration

- **Responsibility for data and safety monitoring**

The PI (unmasked) will monitor the data and any adverse events, which will in turn be reported to the University of Houston Committee for Protection of Human Subjects and the NEI Program Officer. This collective body of individuals will ultimately be responsible for monitoring the trial.

- **Frequency of DSM**

There will be no formal review of the data over the course of the trial, but the PI will be continuously involved in verifying the completion and accuracy of data entry, as well as the occurrence of adverse events.

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