**Dilated Versus Non-Dilated Wavefront Corrections for Patients with Down Syndrome**

**NCT# 05059041**

**9/15/2021**

## Research Protocol

*Dilated Wavefront versus Non-Dilated Wavefront for Metric-Optimized Refraction Procedure*

***Study Objectives:***

To determine whether dilation can be eliminated as part of the process to identify spectacle refractions from wavefront aberration measures.

We will test the following hypothesis:

1. Differences between refractions determined pre and post dilation are within the repeatability of subjective refraction (0.62D).
2. Differences between distance acuity obtained through refractions determined pre and post dilation are within the repeatability of acuity testing (7 letters).
3. Participant ratings of vision and refraction preference do not differ between refractions determined pre and post dilation.
4. Differences between near acuity obtained through refractions determined pre and post dilation are within the repeatability of acuity testing (1 line).

***Background and Rationale:***

*Justification*

Identifying the best performing refraction for a patient with Down syndrome can be challenging due to both the elevated optical distortions commonly found in eyes of patients with Down syndrome, as well as the cognitive deficits that make performance of routine clinical tests challenging. The study team has previously investigated the use of objective measurements of the eye's optics (wavefront aberrometry) to determine the refraction predicted to perform the best for the patient (Ravikumar, 2019; Anderson, 2021). The first iteration of our work to identify optimized corrections was based upon post-dilation measures of wavefront aberrations in adults with Down syndrome and subsequent calculation of refractions after the participant's visit concluded. Prior to incorporating this technique in a clinical setting, the calculation of a metric-optimized refraction would ideally occur during the same visit. This would meet the patient expectation that refractions and spectacle prescriptions are provided in a single encounter and it would afford the practitioner the opportunity to evaluate the performance of the refraction prior to finalizing the prescription. Dilation is thus a barrier to the clinical application of this technique and evaluating the use of dilated versus non-dilated wavefront measures for the calculation of metric-optimized refractions is a necessary endeavor to refine this technique for clinical deployment.

It is well established that the magnitude of higher order aberrations increase with increasing pupil diameter (Wang, 2003), and thus the optimal refraction for a given eye could conceivably depend upon pupil diameter, particularly for highly aberrated eyes. In our previous studies we investigated this hypothesis by calculating metric-optimized refractions from dilated measures

of the eyes of 30 adults with Down syndrome re-sized to both 6mm and a 4mm pupil diameters, after which we converted refractions to vector notation and calculated the dioptric difference (Raasch, 2001) between refractions. While some differences between refractions were found (mean difference = 0.26 ± 0.50D), the differences did not exceed the repeatability of clinically utilized subjective refraction techniques (Anderson, 2019). In our clinical trial whereby refractions were dispensed to participants with DS, we dilated the eye to obtain wavefront aberration measures, but identified metric-optimized refractions after re-sizing the images to match the non-dilated, habitual pupil diameter of each individual participant (Anderson, 2021). Using this methodology, we observed good performance of metric-optimized refractions evidenced by the finding that all metric-optimized refractions passed the initial safety check to be dispensed in the trial. This suggests that if wavefront aberrations were measured at the habitual pupil diameter rather than the fully dilated diameter, the method could be equally (and potentially even more) successful.

Dilation not only impacts pupil diameter, but also paralyzes accommodation (the focusing ability of the eye), eliminating the confounding factor of instrument myopia during aberration measures, which could be an argument for maintaining dilation in the methodology. While it is common clinical practice to paralyze accommodation in young children to avoid instrument myopia (a measured increase in myopic refractive error related to the patient increasing the focus of the eyes when looking into a closed-field instrument), the phenomenon is less likely to be observed in patients with Down syndrome who are known to have significant accommodative (focusing) deficits, even in early childhood (Woodhouse, 1993; Anderson, 2011). Additionally, while paralyzing accommodation reveals the full defocus of the eye, it potentially creates new challenges if the patient rejects a more hyperopic correction identified during paralysis of accommodation when the correction is later applied after accommodation resumes. *Based on evidence that pupil diameter was not a significant factor in the determination of metric-optimized refractions for adults with Down syndrome and given that poor accommodative ability is likely to protect against instrument myopia, it is reasonable to hypothesize that dilation can be eliminated in the identification of metric-optimized refractions.*

*Anticipated Results & Potential Pitfalls*

We expect refractions obtained from pre- and post-dilation measures will not differ significantly. The exception could be for participants who have accurate accommodative responses. For these participants, it is anticipated that refractions may differ if the participant exhibits instrument myopia during aberration measures, evidenced by more hyperopic (less myopic) post-dilation refractions. Analysis of dioptric differences by secondary factors, such as accommodative ability, will permit detection of subgroups for whom dilation may be important. In addition, we expect refractions obtained from pre- and post-dilation measures to result in similar acuity performance when tested on study participants through the use of trial frames. One potential problem associated with this metric is that visual acuity measures will be taken with trial frames rather than ground spectacle lenses. Particularly when refractive error is high and significant magnitudes of astigmatism are present, building a prescription in a trial frame becomes challenging in that vertex distance is more difficult to control and reflections from lenses can interfere with performing an acuity task. That said, this is an accepted first step in

evaluating refractions in the clinic, and the necessity of dilation for metric-optimized spectacle prescriptions and producing ground spectacles for this one-time assessment would not be fiscally appropriate. The analysis for this experiment is based upon a comparison of acuity between refractions, and thus both conditions will experience the same challenges and there is unlikely to be a bias toward one type of refraction (pre- versus post-dilation) over the other.

Lastly, we will compare participant ratings and preference of refractions obtained pre- and post-dilation through use of a 5 point rating scale depicting a series of faces from frowning to neutral to smiling. We anticipate no difference in ratings for the two refraction types; however, one challenge with this goal is that participants may be unable to provide adequate discrimination of preferences using the scale. While we did use this scale previously in studies with adult participants, this new study includes children with Down syndrome who may be less cognitively advanced and thus unable to provide responses on such a survey. Although it is possible we will not successfully obtain data from all participants, we feel it is important to attempt to capture subjective feedback regarding the corrections.

*Significance & Potential Benefit*

If this study demonstrates that dilation can be eliminated as part of the optimized refraction process, it will result in a procedure that is much more easily deployed in a clinical setting, resulting in decreased examination time, increased patient comfort, and eliminate the need for a second office visit to finalize the refraction. While there is no direct benefit to the participants in this study, there is the potential for the community at large to benefit, particularly individuals with Down syndrome for whom this refraction strategy may most likely be adopted.

***Procedures:***

*Research Design*

This is an experimental, multi-site, clinical treatment trial with a randomized cross-over design to evaluate two spectacle prescriptions in-office. Treatments will not be dispensed to participants.

*Sample*

The sample size for this study is 20 adults with Down syndrome enrolled at University of Houston College of Optometry and 20 children with Down syndrome enrolled at The Ohio State University College of Optometry. Sample size was calculated for each site separately and is based upon 90% power to detect differences in refractions as small as 0.42D between prescriptions. In addition, a sample size of 20 provides 80% power to identify moderate correlations (0.60 or higher) between refraction differences and demographic factors and clinical characteristics. A sample size of 20 provides power in excess of 99% to detect differences in visual acuity of 7 letters or more between refractions.

Potential participants will be recruited in the following manners:

- Patients at The Ohio State University and University of Houston clinics may be given informational brochures
- Paper flyers may be posted in The Ohio State University and University of Houston clinics
- Paper flyers and brochures may be distributed to the Nisonger Center program facilities, Special Olympics Ohio, and the Down Syndrome Association of Central Ohio
- Electronic announcements may be posted to the college of optometry social media pages for the respective sites
- Email announcements may be distributed to the college of optometry faculty/staff/student/alumni listserves for the respective sites
- Email announcements may be distributed to members of the Nisonger Center programs, Special Olympics Ohio, and the Down Syndrome Association of Central Ohio
- Electronic announcements may be posted on the social media account and the research tab of the website for the Down Syndrome Association of Central Ohio
- Records reviews will be conducted by study personnel to identify potential participants from the college of optometry clinics at the respective sites. Potential participants that are identified through records reviews will be contacted either via email or phone by study personnel using recruitment scripts.

Potential participants will be screened by study personnel at the first study visit for the following eligibility criteria:

- Self (or guardian) reported diagnosis of Down syndrome
- Age of 5 – 17 years (OSU) or minimum age of 18 years (UH)
- Able to be dilated (no medical history contraindicating use of dilation drops, no ocular signs contraindicating use of dilation drops such as narrow anterior chamber angles or elevated IOP)
- No nystagmus (inability to fixate steadily due to involuntarily eye movements)
- No history of intraocular or refractive surgery
- No corneal or lenticular opacities that would hinder wavefront measurements
- No history of ocular disease
- Behaviorally able to fixate for study measures
- Behaviorally able to respond for visual acuity testing

*Measurement*

The refractions used as the treatment in this trial will be determined from mathematical analysis of wavefront measures as previously defined (Ravikumar, 2019). The outcome measures listed below will be used to test the hypotheses.

*Dioptric Difference:* Each of the pre- and post-dilation refractions will be converted to vector notation (three dimensional coordinates) and the dioptric distance between vectors for each refraction calculated to quantify the difference between refractions (Raasch, 2001).

*Distance Visual Acuity:* Visual acuity will be measured for distance viewing with the British Standard Letter set or the four letter (HOTV) set depending upon the participant's cognitive ability. The acuity testing will be performed one eye at a time and then binocularly using a computerized letter presentation during which participants begin with large letters and work down to smaller letters until 5 total mistakes are made. This acuity protocol has previously been utilized with patients with Down syndrome and demonstrated to have a repeatability of approximately 7 letters (Ravikumar, 2018; Anderson, 2021).

*Near Visual Acuity:* Visual acuity will be measured binocularly at 40cm using a plastic card with a four letter set (HOTV). Participants will name or match letters at the largest print size and work down until 50% or more letters of a particular size are identified incorrectly. This test has previously been utilized with patients with Down syndrome and demonstrated to have a repeatability of 1 line (Anderson, 2021).

*Participant Survey:* Participants will be asked to rank vision at each distance and near viewing on a 5 point scale by pointing to a face depicting their feeling about their vision. In addition, participants will be asked to select the refraction that they prefer. Reliability data is not available for this instrument.

*Detailed Study Procedures*

This study will enroll 40 individuals with Down syndrome age 5 years and older for evaluation of refractions calculated from pre-dilation wavefront aberration measures versus refractions calculated from post-dilation wavefront aberration measures. Twenty children with Down syndrome will recruited at The Ohio State University site and 20 adults with Down syndrome will be recruited at University of Houston. This is a lab-based study and the treatment being studied, pre and post-dilated refractions, will not be dispensed to participants outside of the lab study visit. All participants will be tested with both treatments in random order in the lab-setting.

The initial study visit will be conducted by a clinical examiner who will: 1) ask medical and ocular history questions of the participant's parent/guardian, 2) evaluate the participant's eligibility for the study by measurement of vision, eye teaming skills, and ocular health, and 3) assess the participant's safety for dilation. Participants meeting eligibility criteria will have measurements of the focusing ability of the eye and measurements of the optical distortions of the eye (wavefront aberration) taken both prior to and after dilation with clinical dilation drops.

The following is a list of the clinical tests/instruments and estimated test times for the initial study visits.

- Questions regarding participant demographics, medical history, and ocular history (5 minutes)
- Participants identifying letters and shapes to assess visual acuity at both distance and near viewing and depth perception (15 minutes)

- Participants looking at letters, lights, or pictures while an examiner observes the movement of the eyes and the eye teaming skills, such as through covering an eye with a plastic paddle (3 minutes)
- Assessing pupil responses with lights (1 minute)
- Evaluating ocular health through use of a biomicroscope (3 minutes)
- Evaluating ocular pressure through use of a non-contact tonometer (i.e. air puff test) or the EyeCare tonometer (micro probe that does not require ocular anesthetic) (5 minutes)
- Measurement of the refractive power of the eye and focusing ability with the Grand Seiko Autorefractor as participants view pictures or letters at both distance and near (non-invasive commercially available instrument that measures the eye using infrared light) (4 minutes)
- Measurement of the wavefront aberrations of the eye with the COAS Wavefront aberrometer (non-invasive commercially available instrument that measures the eye using infrared light) (10 minutes)
- Dilation of the eyes using 1% tropicamide and 2.5% phenylephrine (5 minutes)
- Repeated measurements with the Grand Seiko autorefractor and COAS Wavefront aberrometer 30 minutes post dilation (14 minutes)

The total time for visit 1 is anticipated to be 1.5 hours.

Following the initial study visit, the investigator will use software designed to identify the optimum spectacle prescription of the eye (i.e. the prescription that is predicted to provide the best focus of light on the retina) for both the images obtained pre-dilation as well as the images obtained post-dilation. Next, participants will return for a second study visit to perform subjective testing with each refraction. Both the pre- and post-dilation refractions will be evaluated in random order through the use of a trial frame with loose lenses. Refractions will not be produced into standard spectacle frames. An un-masked investigator will build each trial frame and disguise the spectacle powers with tape over the lens handles. An investigator who is masked to the refraction in the trial frame will conduct visual acuity testing on the participant for distance and near viewing, followed by asking the participant to rate their vision on a five point scale. Testing will be repeated with the other refraction on the same day. Following acuity and subjective rating testing, participants will be asked to compare the two refractions and select the one they rate best.

The following is a list of the clinical tests/instruments and estimated test times for the second study visit.

- Participants identifying letters and shapes to assess distance and near visual acuity and depth perception with each refraction (30 minutes)
- Measurement of the refractive power of the eye and focusing ability with the Grand Seiko Autorefractor as participants view pictures or letters at both distance and near

(non-invasive commercially available instrument that measures the eye using infrared light) (4 minutes)
- Participants completing a survey rating each refraction (termed the 'Smile Survey' for this study – attached later in this submission) (5 minutes)
- Participants making a direct comparison between the two refractions to select their preferred refraction (5 minutes)

The total time for visit 2 is estimated to be 40 minutes.

*Study Risks*

The risks involved in participation in this study are no greater than that incurred during a routine eye examination with dilation. Participants will be screened for safety to dilate and will not pass the eligibility criteria evaluation if they have indications of narrow anterior chamber angles or medical conditions and/or medication use that would contraindicate the use of dilation drops. While IOP measures will be attempted as the gold standard of care prior to dilation, obtaining these measures on all participants may not be possible due to behavioral challenges related to intellectual disability. Dilation without IOP measures is still common clinical practice for pediatric patient populations and/or those with intellectual disability. Given these precautions, the likelihood of an adverse event from dilation is extremely low. For participants who do experience an adverse event, care can be sought through the site clinics as disclosed in the parental permission document. All other study procedures are non-invasive and only involve lights as the participant places his/her chin on a chinrest and looks straight ahead. Some participants, particularly children, may find the tasks boring or challenging, but participants will be given breaks and time allotted during study visits to work at the pace of the participant.

*Data Collection and Participant Confidentiality*

Data collected for this study on commercial instruments (autorefractor, wavefront aberrometer) will be stored using unique study IDs for each participant that do not contain personally identifiable information. For instruments requiring a birthdate, only the participant's birth year will be input. Printouts from instruments will be scanned and stored under the participant's unique study ID on the PI's secure network storage. Medical history data and other clinical findings will be recorded directly into REDCap and stored using only the unique study ID and no personally identifying information. The link between the identifier and the participant's personal information will be maintained with the signed consent documents in a locked lab accessible only to the study team at each site. This personal information will be stored for no more than 3 years after completion of data collection and analysis for the study.

*Internal Validity*

The order of refraction testing will be randomized at study visit 2. Study personnel who are not participating in the testing will prepare the trial frames in advance and tape over the handles to mask the powers of the lenses to both the patient and the investigator conducting the testing. Both the investigator administering the acuity testing and survey, as well as the study

participant, will be masked to the refraction being tested. Testing distance for acuity will be measured and monitored throughout testing.

*Data Analysis*
We will report descriptive statistics for all demographic and clinical measures. All analyses will be completed using SAS version 9.4 (Cary, NC).

Research hypothesis 1: Dioptric difference pre- and post-dilation
A one-sample t-test will be used to compare the dioptric difference in refractions obtained pre- and post-dilation to 0.62 (clinically relevant). Additionally, the impact of various demographic and clinical measures on the observed dioptric difference will be assessed using regression analyses. Potential covariates include participant age, refractive error magnitude and type (e.g. myopia vs. hyperopia), accommodation (Grand Seiko autorefractor measures), and higher order RMS. If necessary based on distribution of dioptric difference values, non-parametric regression analysis methodology will be utilized.

Research hypothesis 2: Binocular visual acuity at distance
Comparison of visual acuity in each metric-optimized refraction type (pre- or post-dilation) will be completed using a dependent t-test. As with dioptric difference, regression analyses will be used to test the association of difference in visual acuity and the demographic and clinical measures investigated in earlier modeling.

Research hypothesis 3: Subjective satisfaction with refraction
Subjective satisfaction outcome (pictorial scale ranging from very unhappy to very happy) will be dichotomized for statistical analysis. An initial comparison of these responses after wear of each refraction will be done using a McNemar's test. Generalized estimating equations (GEE) will be used to identify any demographic or clinical measures that might impact the agreement of the subjective quality outcome.

Research hypothesis 4: Binocular visual acuity at near
Comparison of visual acuity in each metric-optimized refraction type (pre- or post-dilation) will be completed using a dependent t-test. As with dioptric difference, regression analyses will be used to test the association of difference in visual acuity and the demographic and clinical measures investigated in earlier modeling.

**Bibliography**

Anderson HA, Manny RE, Glasser A, Stuebing KK. Static and dynamic measurements of accommodation in individuals with down syndrome. *Invest Ophthalmol Vis Sci*. 2011;52(1):310-7. PMCID: PMC3053281.

Anderson HA, Benoit JS, Marsack JD, Manny RE, Ravikumar A, Fern KD, Trast KR. A randomized trial of objective spectacle prescriptions for adults with Down syndrome: Baseline data and methods. *Optom Vis Sci.* 2021; 98:88-99. PMCID: In-progress.

Raasch TW, Schechtman KB, Davis LJ, Zadnik K, CLEK Study Group. Repeatability of subjective refraction in myopic and keratoconic subjects: results of vector analysis. *Ophthal Physiol Opt*. 2001;21(5):376-83.

Ravikumar A, Benoit JS, Morrison KB, Marsack JD, Anderson HA. Repeatability of monocular acuity testing in adults with and without Down syndrome. *Optom Vis Sci*. 2018;98:202-11. PMCID: PMC5822740.

Ravikumar A, Benoit JS, Marsack JD, Anderson HA. Image quality metric derived refractions predicted to improve visual acuity beyond habitual refraction for patients with Down syndrome. *Transl Vis Sci Techn*. 2019;8(3):20. PMCID: PMC6532430.

Wang Y, Zhao K, Jin Y, Niu Y, Zuo T. Changes of higher order aberration with various pupil sizes in the myopic eye. *J Refract Surg*. 2003;19:S270-4.

Woodhouse JM, Meades JS, Leat SJ, Saunders KJ. Reduced accommodation in children with down syndrome. *Invest Ophthalmol Vis Sci*. 1993;34(7):2382-7.