CORRECTION OF MYOPIA EVALUATION TRIAL

COMET2

A randomized trial of the effect of progressive addition lenses versus single vision lenses on low myopia associated with large accommodative lags and near esophoria in children

PROTOCOL

Version 3.0

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CORRECTION OF MYOPIA EVALUATION TRIAL (COMET2)
A randomized trial of the effect of progressive addition lenses versus single vision lenses on low myopia associated with large accommodative lags and near esophoria in children
PROTOCOL AMENDMENT 7-18-05

This amendment provides for the following two protocol changes:

Protocol Change #1

Current Protocol
Currently the refractive error criteria for eligibility for screening with cycloplegic autorefraction and the refractive error criteria for eligibility for the randomized trial, both include the criterion of anisometropia ≤ 0.50 D difference between eyes in spherical equivalent.

Proposed Change
The proposed change is to widen the amount of allowable anisometropia in both eligibility criteria to anisometropia ≤ 1.00 D difference between eyes in spherical equivalent.

Rationale for Change
The study's original inclusion criterion had been specified as anisometropia <= 1.00 D for consistency with the criterion used in the original COMET study, but was later changed (prior to the study's start) to anisometropia <= 0.50 D for consistency with the amblyopia studies conducted by the PEDIG network. In retrospect the change had been ill-advised because in the amblyopia studies the criterion is used to define anisometropia *as a cause of ambylopia* in primarily hyperopic children, whereas in the COMET2 the purpose of the criterion is to define a permissible amount of anisometropia in patients with low myopia. Therefore, it is felt preferable that the COMET2 criterion be changed to <= 1.00 D for consistency with the original COMET study.

Protocol Change #2

Current Protocol
The current protocol indicates that whenever a prescription change is made, either by protocol or at investigator discretion, that the *amount of the change* in correction is at investigator discretion.

Proposed Change
Whenever spectacles are changed, either by protocol or at investigator discretion, the endpoint of the subjective refraction should be prescribed.

Rationale for Change
Because at enrollment spectacles are being prescribed according to the endpoint of the subjective refraction and because it would be usual practice in spectacle changes to prescribe the endpoint of the subjective refraction, it was felt that the protocol should require all spectacle changes be prescribed as such.

CORRECTION OF MYOPIA EVALUATION TRIAL 2 (COMET2)
A Randomized Trial of the Effect of Progressive Addition Lenses Versus Single Vision Lenses on Low Myopia Associated with Large Accommodative Lags and Near Esophoria in Children
PROTOCOL AMENDMENT #2 (3-9-06)

This amendment provides for a protocol change to the randomized trial eligibility criterion for accommodative response. The criterion for accommodative response will be lowered by 0.50 D, therefore requiring a higher amount of accommodative lag for randomized trial eligibility.

Current Protocol

The current protocol specifies that patients are eligible for the randomized trial if their accommodative response at 33 cm (3.0 D) is less than 2.50 D (i.e., lag of accommodation 0.50 D or greater) as measured by non-cycloplegic autorefraction with a Grand Seiko open field of view autorefractor.

Proposed Change

The proposal is to narrow the randomized trial eligibility criterion for accommodative response to less than 2.00 D (lag of accommodation 1.0 D or greater) therefore requiring a higher amount of accommodative lag for randomized trial eligibility.

Rationale for Change

We now have reason to believe that the accommodative response measured by the method used in the current study is less than the accommodative response measured by the method used in COMET, the study on which the rationale for COMET2 is based. The major difference between the two methods of measuring accommodative response is the autorefractor. A Canon R-1 was used in the COMET study whereas the COMET2 uses a Grand Seiko, a newer autorefractor which is more accurate than the Canon R-1. Another difference is that in COMET, an eye was tested while a Maddox rod and Risley prism were held in front of the other eye (allowing for simultaneous measurement of phoria), whereas in COMET2 an eye is tested while an occluder is held in front of the other eye. Results from a pilot study of 40 myopic young adults found that the accommodative response measured by the COMET2 method was 0.35 D less than by the COMET method, meaning that the accommodative lag was greater by the same amount. Therefore, COMET2 is very likely enrolling some patients with larger accommodative response (i.e. less accommodative lag) than that of COMET patients in the subgroup which showed a clinically meaningful treatment effect of PALs.

While the results of the pilot study support reducing the lower limit of accommodative response to 2.15 D, it was decided to reduce the limit further to 2.00 D for two reasons. The first reason relates to the future ability of clinicians in the community to implement the definition of high accommodative lag, as clinicians normally measure accommodative response using monocular estimation method (MEM) retinoscopy or Nott retinoscopy, the former of which measures accommodative lag in quarter-diopter steps. Second, adopting a threshold of 2.00 D helps to ensure that COMET2 will enroll children who truly have higher accommodative lags.

Impact of Change

Recruitment

Because sample size for the primary analysis was based on enrolling 100 patients, the study now plans to recruit 100 patients whose accommodative response is in the range required under the new threshold, up to a maximum of 150 patients total.

Informed Consent

No changes will be needed to the informed consent or assent documents.

Existing Randomized Patients Not Meeting Revised Criterion

Approximately 25% of the patients randomized thus far have accommodative response which exceeds the revised criteria. The proposal is that such patients continue in the study, masked, and in their assigned treatment groups. There is no reason to think that patients with less accommodative lag wouldn't benefit from treatment, even though they might not be expected to have the same degree of treatment benefit as would patients with higher amounts of lag. Also, there are no unique safety concerns related to patients with lesser amounts of accommodative lag wearing PALs, in fact, some clinicians prescribe PALs to similar patients in their routine practices based solely on the presence of esophoria.

Although these patients will be able to continue in the study, given that they were consented into the study on the basis of their having certain characteristics including high accommodative lag, it is felt that some form of disclosure is warranted. At the patient's next study visit, the investigator will inform the patient and parent that the patient may not have as much difficulty focusing (accommodating) as was previously thought. In addition to verbally conveying this information, parents will be given a written IRB-approved disclosure statement. Parents and patients will be encouraged to have the patient stay in the study but will have the option to withdraw. Masking of treatment group will be maintained regardless of whether the patient continues in the study or opts to withdraw.

Primary Analysis

The primary analysis will include data from all randomized patients, regardless of whether the patient meets the revised accommodative response criterion.

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CHAPTER 1: BACKGROUND AND SUMMARY

1.1 Objective

The principal objective of this randomized trial is to determine if progressive addition lenses (PALs) versus single vision lenses (SVLs) slow the progression of low myopia in children with poor accommodative responses (i.e., large accommodative lags) and near esophoria.

1.2 Rationale

Myopia is a significant public health problem that affects at least 25% of adults in the United States and a much higher percentage of people in Asia. It is a predisposing factor for retinal detachment, myopic retinopathy, and glaucoma, thus contributing to loss of vision and blindness. As might be expected for such a prevalent condition, treatment costs are high. If interventions to retard myopia progression are successful, sight-threatening complications might be avoided and costs should be reduced.

At present, the mechanisms involved in the etiology of myopia are unclear and methods for prevention are unproven. Even without a sound scientific rationale, many options for slowing the progression of myopia have been evaluated. Results of studies using spectacle lenses, mainly bifocals and PALs vs. SVLs, have been equivocal. In addition, compared to SVLs, bifocals and PALs are more expensive and their long term effect on accommodation is unknown.

The overall 3-year difference in progression between children wearing PALs vs SVLs in the Correction of Myopia Evaluation Trial (COMET) was 0.20D, statistically significant but not clinically meaningful.[1]

Reduced accommodative responses in association with near work has been shown in previous research to be a factor in the development and progression of myopia.[2-4] The COMET study found in a secondary analysis that children with larger accommodative lags (> 0.43D for a 33 cm target, based on a median split) wearing single vision lenses (SVLs) had the most progression at 3 years, and that progressive addition lenses (PALs) were effective in slowing progression in these children, with statistically significant adjusted 3-year treatment effects for those with larger lags in combination with near esophoria (0.64D), or lower baseline myopia (0.48D).[5] The treatment effects also were observed in these groups at 1 year and became larger from 1-3 years. These results suggest that PALs are a clinically-viable spectacle treatment for slowing progression in myopic children with large accommodative lags in conjunction with near esophoria and lower amounts of myopia.

1.3 Synopsis of Study

Screening / Eligibility

Patients aged 8 to <12 years old who are suspected of having myopia in the range of –0.50D to - 3.00D will be invited to be screened for the randomized trial.

The screening procedures will be explained and the parent or guardian of each patient will give written informed consent for screening before any screening-specific procedures are performed. Approximately 700 children are expected to be screened.

Screening consists of non-cycloplegic procedures of subjective refraction, testing of oculomotor alignment, and testing of accommodative response. Measurement of accommodative response using the Grand Seiko autorefractor is part of the screening for the randomized trial. Patients at participating sites also will be asked to complete two additional tests of accommodation by MEM and Nott retinoscopy as part of an ancillary study.

Once the above non-cycloplegic screening procedures are completed, patients who are ineligible for the randomized trial will terminate participation in the study. Patients who *appear to be eligible* for the randomized trial then will undergo cycloplegic autorefraction to determine whether refractive error in each eye is within the eligibility range of -0.75 to -2.50 D spherical equivalent.

Once the patient's eligibility has been verified by cycloplegic autorefraction, the trial will be further discussed with the patient's parent or guardian and written informed consent for the randomized trial will be obtained.

A summary of the screening/enrollment process is shown in the flowchart in section 1.4.

Randomization

Each patient entering the randomized trial will be randomly assigned to one of two treatment groups: Progressive addition lenses (PALs) with a +2.00 D addition, or single vision lenses (SVLs). Spectacles will be prescribed and paid for by the study.

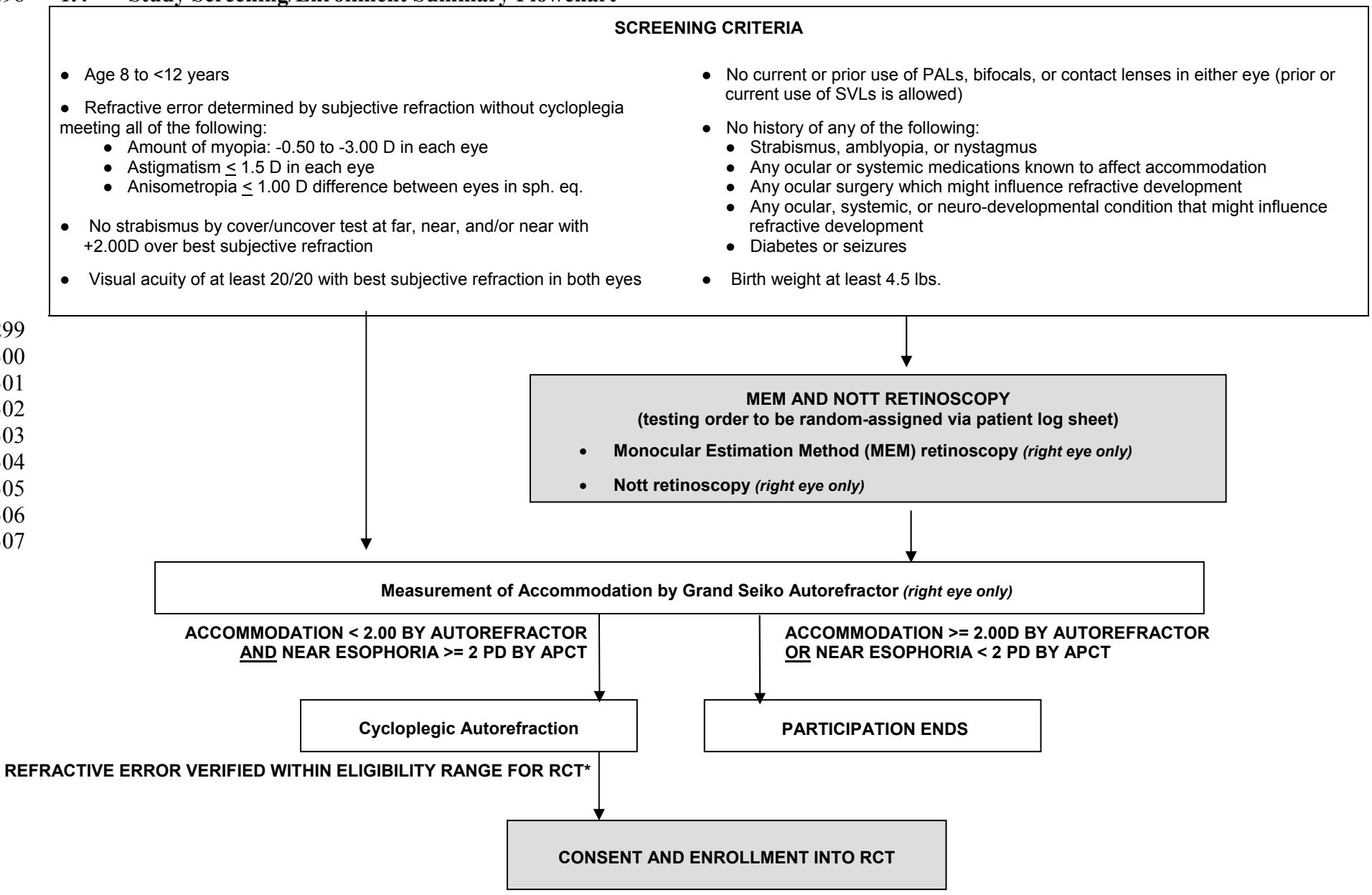
The sample size for the primary analysis for the trial is estimated to be 100 children, with approximately half of the children randomized to PALs and the other half randomized to SVLs.

Follow-up

Children will have three years of follow up, with visits every 6 months. At each visit a subjective refraction will be performed to assess whether a prescription change is needed, accommodative response will be measured using an open field autorefractor, and oculomotor alignment will be assessed. At the one-, two-, and three-year visits, the primary outcome measurements of cycloplegic autorefraction will be taken.

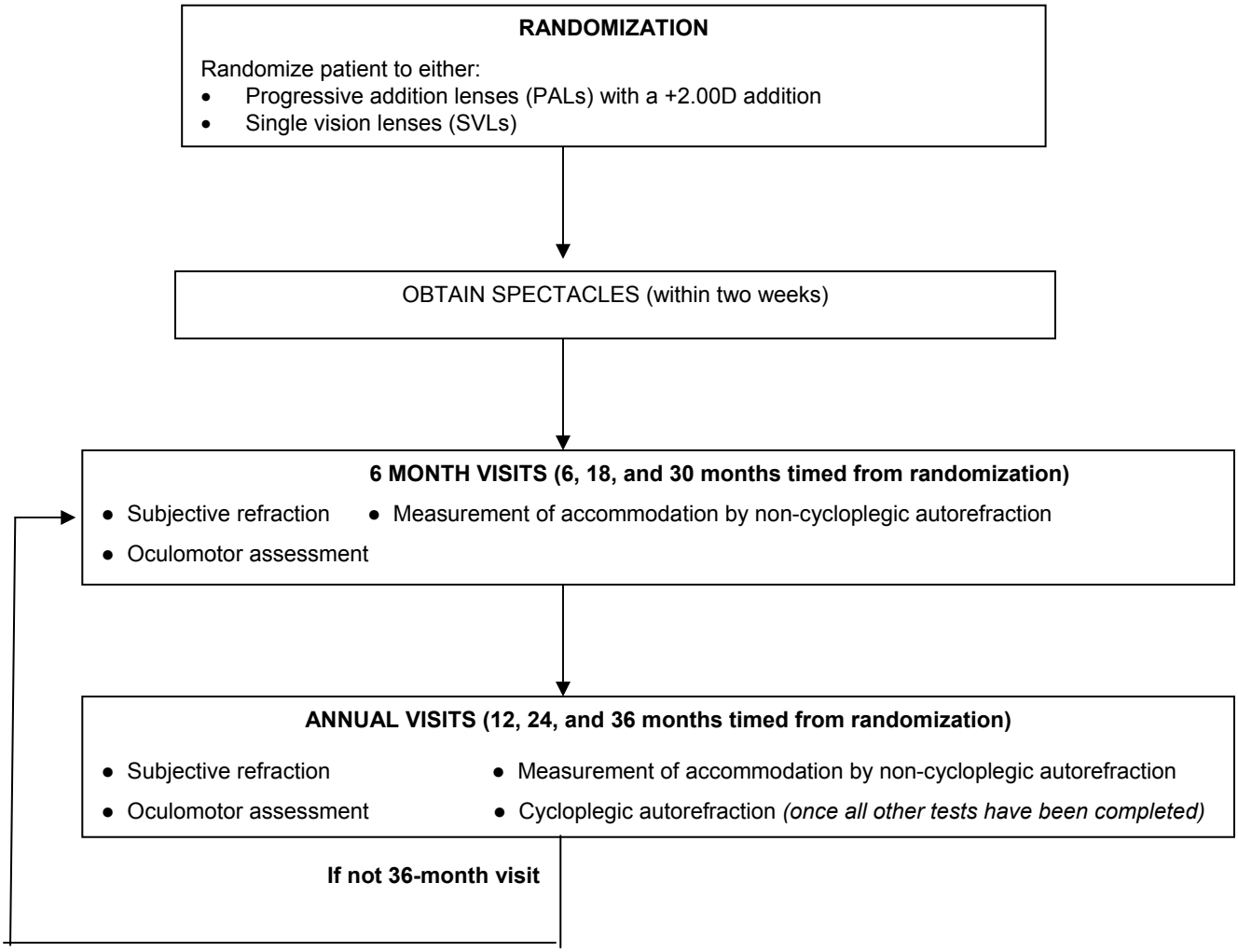
A summary of the randomized trial is shown in the flowchart in section 1.5.

1.4 Study Screening/Enrollment Summary Flowchart



*Refractive error by autorefraction with cycloplegia meeting all of the following: amount of myopia: -0.75 to -2.50 D in each eye, astigmatism ≤ 1.5 D in each eye, and anisometropia ≤ 1.00 D

1.5 Randomized Trial Summary Flowchart



CHAPTER 2: SCREENING/ENROLLMENT

2.1 Eligibility Assessment and Informed Consent

Patients aged 8 to <12 years old who are suspected of having myopia in the range of –0.50D to - 3.00D will be invited to be screened for the randomized trial.

The screening procedures will be explained to the parent or guardian of each patient, and he/she will give written informed consent for screening before any screening-specific procedures are performed. Approximately 700 children are expected to be screened.

Because fewer than 15% of screened children are expected to be eligible for the randomized trial, the non-cycloplegic screening procedures will be performed first and only patients who appear eligible for the randomized trial based on these procedures will undergo cycloplegia and subsequent autorefraction.

Screening consists of subjective refraction, testing of oculomotor alignment, and testing of accommodation. Measurement of accommodative response using the Grand Seiko autorefractor is part of the screening for the randomized trial. Patients at participating sites will be asked to complete two additional tests of accommodation by MEM and Nott retinoscopy as part of an ancillary study.

Once the non-cycloplegic screening procedures are completed, patients who are ineligible for the randomized trial will terminate participation in the study. Patients who *appear to be eligible* for the randomized trial will undergo cycloplegic autorefraction to determine whether refractive error in each eye is within the eligibility range of -0.75 to -2.50 D spherical equivalent.

Once the patient's eligibility has been verified by cycloplegic autorefraction, the trial will be discussed with the patient's parent or guardian and written informed consent for the randomized trial will be obtained.

2.2 Screening

The Screening/Enrollment Form should be completed on the PEDIG website or by faxing the form to the Jaeb Center if internet access is down.

Screening of potentially eligible patients will included collection of historical information including date of birth, gender, ethnicity, spectacle prescription, diagnosis of significant eye disease, eye surgery, systemic diseases, and medication use.

For screening procedures, non-cycloplegic screening procedures will be performed first (see section 2.1.1), then if the patient appears to be eligible for the randomized trial based on non-cycloplegic procedures (see section 2.2.2), cycloplegic autorefraction will be performed to verify randomized trial eligibility (see section 2.2.3).

2.2.1 Non-cycloplegic Procedures

The following procedures should be performed without cycloplegia:

1. Subjective refraction in both eyes
   - The subjective refraction should be performed in both eyes prior to all other screening procedures, as the results of this assessment will determine:
     - The appropriate correction to use for the oculomotor assessment and measurement of accommodative response.
     - The spectacle correction to be prescribed if the patient is eligible for the randomized trial.
   - The protocol for this procedure is described in the Testing Procedures Manual.

2. Measurement of accommodative response at near in the right eye using MEM and Nott retinoscopy, if the patient is participating in the ancillary study of these procedures (see chapter 5)

3. Measurement of accommodative response at near in the right eye using Grand Seiko open field autorefractor
   - Measurements should be taken in the right eye only
   - Measurements will be taken without cycloplegia and using trial frames with the spherical equivalent correction derived from subjective refraction (one lens) in trial frames in front of the right eye and an occluder in front of the left eye
   - The protocol for this procedure is described in the Testing Procedures Manual.

3. Oculomotor assessment

   The following oculomotor assessments will be performed:
   - Cover-uncover test
   - Alternate Prism and Cover Test (APCT)

   Both assessments should be performed as follows, without cycloplegia, using the specified correction in trial frames:
   - At distance and at near using correction determined from non-cycloplegic subjective refraction
   - At near with +2.00D over correction determined from non-cycloplegic subjective refraction

The protocols for these procedures are described in the Testing Procedures Manual

2.2.2 Eligibility for Screening with Cycloplegic Autorefraction

Patients are eligible to continue screening if all of the following are met:

1. Refractive error determined by subjective refraction which meets all of the following:
   - Spherical equivalent: -0.50 to -3.00 D in both eyes
   - Astigmatism $\leq$ 1.5 D in both eyes
   - Anisometropia $\leq$ 1.00 D difference between eyes in spherical equivalent
2. Visual acuity is at least 20/20 with best subjective refraction in both eyes
3. Accommodative response at near (33 cm) is less than 2.00D by non-cycloplegic autorefraction

4. No strabismus present by cover-uncover test at far, near, and/or near with +2.00D over best subjective refraction

5. Near esophoria (≥ 2.0 PD) present by alternate prism and cover test (APCT) at near using best refractive correction determined from non-cycloplegic subjective refraction

6. No current or prior use of PALs, bifocals, or contact lenses in either eye (prior or current use of SVLs is allowed)

7. No history of any of the following:
   - Strabismus
   - Amblyopia
   - Nystagmus
   - Ocular, systemic, or neuro-developmental condition that might influence refractive development
   - Ocular surgery which might influence refractive development
   - Ocular or systemic medications known to affect accommodative response, such as atropine, pirenzepine, and anti-epileptic medications
   - Diabetes or seizures

8. Birth weight at least 4.5lbs

2.2.3 Cycloplegic Autorefraction

If the patient is eligible for screening with cycloplegic autorefraction, this procedure will be performed on both eyes using the Grand Seiko autorefractor after cycloplegia with 2 drops of 1% tropicamide.

- The protocol for this procedure is described in the Testing Procedures Manual.

Patients are considered eligible for the randomized trial if the refractive error obtained by cycloplegic autorefraction meets all of the following:

- Spherical equivalent: -0.75 to -2.50 D in each eye
- Astigmatism ≤ 1.5 D in each eye
- Anisometropia ≤ 1.00 D difference between eyes in spherical equivalent

2.3 Randomization

Each patient enrolling in the randomized trial will be randomly assigned to one of two treatment groups:

- Progressive addition lenses (PAL) with a +2.00D addition
- Single vision lenses (SVL)

The JAEB Center will construct a master randomization list using a permuted block design stratified by site and by whether the patient has previously worn spectacles, which will specify the order of treatment group assignments.

The patient's treatment group assignment can be obtained either by completing randomization on the PEDIG website or by contacting the Jaeb Center if internet access is down.

2.4 Prescribing Spectacles

Spectacles will be prescribed according to the endpoint of the subjective refraction (i.e. minimum minus for best acuity).

2.5 Obtaining Spectacles

Patients will be sent to a study-certified optician to have the spectacles made and fitted.

Spectacles will be provided at no cost to the patient

- All lenses (i.e. single-vision and progressive-addition) will be polycarbonate and will be donated by Essilor.
- The frames will be paid for by the study.

Specific fitting protocols detailed in the Testing Procedures Manual will be used for fitting PALs and SVLs.

Patients should be encouraged to obtain the new spectacles within 2 weeks of randomization.

CHAPTER 3: FOLLOW-UP

3.1 Visit Schedule

Patients will have protocol-specified follow-up visits every six months (± 2 weeks) for three years. Visits will be timed from the date of randomization.

Additional visits may be scheduled as needed (see section 3.2).

3.2 Protocol Visits

3.2.1 Examination Procedures

Prior to the patient's examination by the investigator, the clinic coordinator will update the child's history, and will verify the spectacle prescription using a lensometer.

The following procedures will be performed without cycloplegia and by the same methods as were used at the enrollment visit:

1. Subjective refraction of both eyes
    - The purpose of the subjective refraction is to determine whether the patient's spectacle prescription should be changed (see section 3.4.1).
        - If the investigator is changing the spectacle correction, the subsequent testing at this visit will be performed with the patient wearing the correction to be prescribed.

2. Oculomotor assessment using cover-uncover test and Alternate Prism and Cover Test (APCT) (see section 2.4.1)
    - Both assessments should be performed as follows, without cycloplegia, using the specified correction in trial frames:
        - At distance and near, using the specified correction*
        - At near with +2.00D over the specified correction*

3. Measurement of accommodative response in the right eye by using Grand Seiko open field autorefractor
    - Measurement will be taken with patient wearing trial frames with the specified correction* in front of the right eye and an occluder in front of the left eye.

*The specified correction is the patient's current correction unless the spectacle correction is being changed at this visit, in which case it is the new spectacle correction.

The protocols for the above examination procedures are described in the Testing Procedures Manual.

3.2.1.1 Additional Procedure at Annual Visits

At annual visits, cycloplegic autorefraction of both eyes will be performed using the Grand Seiko autorefractor after administration of 1% tropicamide.

Cycloplegic autorefraction should be performed after all other examination procedures have been completed.

3.2.2 Masking of Treatment Group

At all visits, the investigator will be masked to the patient's treatment group. Patients will remove their spectacles prior to the exam and will not wear the spectacles for any exam procedures.

3.3 Additional Visits

In order to maintain masking of the study investigator, any time the patient reports any type of problem (e.g. blurry vision, headaches, etc.), a visit should be scheduled for an examination by an unmasked consulting clinician.

The procedures and assessments to be completed for this examination are at the discretion of the consulting clinician. A subjective refraction can be performed if the consulting clinician suspects that the refractive error may not be optimally corrected. Other clinical procedures as outlined in the protocol can be used to assess the nature of the problem and to arrive at a viable treatment.

The patient's spectacle prescription may be changed if indicated (see section 3.4.1). On rare occasions in which the patient's problem is not resolved by a change in spectacle prescription, and the consulting clinician feels that a change in lens type (i.e. treatment crossover) may be warranted, the consulting clinician should contact the protocol chair to discuss the case. Prescribing a change in lens type will be permitted only with prior approval of the protocol chair.

3.4 Treatment During Follow Up

The patient should wear the random-assigned spectacles during all waking hours. Contact lenses should not be worn.

Vision therapy may not be prescribed.

3.4.1 Prescription Changes

A prescription change must be made if the subjective refraction finding differs from the current prescription by at least 0.50 D in spherical equivalent. Prescription changes can be made for smaller differences at investigator discretion if the new prescription improves the patient's visual acuity by at least one line over that in their current spectacle correction. Whenever a spectacle change is made, spectacles will be prescribed according to the endpoint of the subjective refraction (i.e. minimum minus for best acuity).

All prescription changes will be documented and tracked.

For progressive addition lenses, prescription changes apply to distance correction only; the power of the addition will remain constant (i.e., +2.00D) throughout the study.

CHAPTER 4: MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

4.1 Patient Withdrawals

A patient (and in this case the parents or guardians) may withdraw from the trial at any time. Based on the high retention (98.5% after 3 years) in COMET1, patient withdrawal is expected to be very infrequent. If the parents or guardians indicate that they want to withdraw the child from the study, the investigator personally should attempt to speak with them to determine the reason.

4.2 Discontinuation of Study

A patient who is found to be ineligible for the study or for whom there are substantial deviations from the protocol may be discontinued from the study. The patient may continue to receive necessary clinical care from the investigator or care may be transferred to another clinician with the consent of the parents.

The study may be discontinued by the Steering Committee (with approval of the Data and Safety Monitoring Committee) before all patients have completed the protocol-specified period of follow up.

4.3 Risks of Examination Procedures

The procedures in this study are part of routine eye care in the United States and pose no known risks. As part of a routine usual-care exam, the patient may receive cycloplegic/dilating eye drops.

4.4 Risks of Treatment

Any type of spectacle wear has a minimal risk for injuries related to frames/lens breakage. Single-vision lenses are routinely prescribed for nearsighted children and pose no additional known risks. The risks of wearing progressive addition glasses are largely unknown. Some children may have some difficulty in the first week with reading, going down steps, and seeing things off to the side. It is not known whether wearing this type of glasses for a long period of time has an effect on accommodative response.

The risks of wearing either type of spectacles are the same as those that would be present wearing the given type of spectacles outside of the study.

4.5 Reporting of Adverse Events

1. A diagnosis of tropia, occurrence of double vision, and any injuries related to frames/lens breakage are to be recorded on the Follow-up Examination Form.

2. Each investigator is responsible for informing his/her IRB of serious treatment-related adverse events and abiding by any other reporting requirements specific to his/her IRB.

3. Data on the complications of study treatment will be tabulated regularly by the Coordinating Center for review by the Steering Committee. Serious complications will be reported expeditiously to the Data and Safety Monitoring Committee, which will receive a full adverse

event report semi-annually. Following each DSMC data review, a summary will be provided to IRBs.

4.6 Patient Payments

Each patient screened for the study will be given a gift certificate valued at $10, regardless of their participation in the ancillary study or their eligibility for the randomized trial.

For patients who are eligible for the randomized trial and elect to participate, the following payments will be made to the parent/guardian:

- $25 for enrollment into the randomized trial
- $25 for completion for each follow-up visit, up to a maximum of $150

If there are extenuating circumstances, additional funds may be provided for travel if expenses exceed $25 and the patient will be unable to complete the visit without the reimbursement of the travel expenses.

4.7 Contacts by the Jaeb Center for Health Research

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent/guardian's contact information. Contact information will be used for issuing payments and for making phone contacts when necessary to facilitate visit scheduling. A patient newsletter, study updates, and a study logo item may be sent. Patients will be provided with a summary of the study results in a newsletter format after completion of the study by all patients.

CHAPTER 5: MEM AND NOTT ACCOMMODATION ANCILLARY STUDY

5.1 Overview

As part of screening to identify patients eligible for the randomized trial, patients at participating centers will be asked to participate in an ancillary study consisting of testing of accommodative response by MEM and Nott retinoscopy before completing the screening measurement of accommodative response by Grand Seiko autorefraction. Recruitment for the ancillary study will continue as part of screening for the randomized trial until 300 patients have been enrolled into the ancillary study.

Patients do not need to participate in the MEM and Nott accommodation study in order to enter the randomized trial. Also, many patients in the MEM and Nott accommodation study will not be eligible for the randomized trial and will end their study participation with the initial visit.

Consent for this ancillary study is covered in the informed consent for screening for the randomized trial.

5.2 Objectives

The objectives of the study are to compare the following measurements of accommodative response obtained by the following methods:

- Monocular Estimate Method (MEM) retinoscopy vs. Grand Seiko autorefractor
- Nott retinoscopy vs. Grand Seiko autorefractor
- Monocular Estimate Method (MEM) retinoscopy vs. Nott retinoscopy

5.3 Rationale

If the randomized trial finds that progressive-addition lenses (PALs) slow myopia progression to a clinically significant degree in children with reduced accommodative response, a new challenge will arise in clinical practice: how to identify such children as candidates for treatment with PALs.

Little data are available on the accuracy of the two clinical techniques that are used by some practitioners to measure accommodative response: Monocular Estimation Method (MEM) retinoscopy and Nott retinoscopy. Autorefractors such as the Grand Seiko open-field autorefractor provide an objective measurement of accommodative response but these instruments are available in few practices due to their high cost. Thus, the current ancillary study is being undertaken to compare data obtained using clinical measures of accommodative response--MEM and Nott retinoscopy--to objective measurements obtained with the Grand Seiko autorefractor.

The aim is to help determine whether a simple, effective measure exists that can be easily used by clinicians to identify children with reduced accommodative response who, if they have low myopia and esophoria, might benefit from treatment with PALs.

5.4 Background

The fundamental strategy in both the MEM and Nott retinoscopy techniques is to provide a subject with a near target (e.g. words at a distance of 33 cm) that is viewed binocularly.

Retinoscopy is then used to determine how closely the subject's accommodative response approximates the accommodative demand created by the target, and, to determine the amount of under-accommodation (lag) or over-accommodation (lead).

In the Monocular Estimate Method (MEM),[6] the reading target is mounted on the retinoscope and has a hole through which retinoscopy is performed. Spherical lenses are introduced briefly in front of one eye to neutralize the perceived motion. This technique assumes that accommodative response is maintained by the other eye while the lenses are introduced and that the lenses are introduced for no more than 300 msec, less than the latency of the accommodative response.

In Nott retinoscopy, the reading target is held at a fixed distance and the clinician performs the retinoscopy slightly off-axis, moving the retinoscope closer to, or farther from the subject to neutralize the reflex. The amount of accommodative response is calculated from the distance at which the neutral motion occurs and is interpreted with regard to the accommodative demand created by the target.

MEM retinoscopy is more commonly referenced in the literature than Nott retinoscopy, and may be simpler to perform because the distance of the target/retinoscope from the subject is fixed. However, the examiner must be sure that the lenses are inserted and removed very quickly so as not to alter the accommodative response. In adults, Nott retinoscopy has been reported to have higher inter-observer agreement[7] and to provide higher values of accommodative lag than MEM retinoscopy.[8]

5.5 Eligibility Criteria

The eligibility criteria are the same as for the randomized trial except for the following:

- Eligibility criterion for amount of myopia is refractive error in the range of –0.50D to -3.00D spherical equivalent by subjective refraction.
- There is no eligibility criterion related to the amount of accommodative response, as the study aims to test children with a wide range of accommodative responses.
- There is no eligibility criterion related to presence of and/or amount of esophoria

5.6 Procedures

The MEM measurements and the Nott retinoscopy measurements must be taken by different study-certified examiners, with each examiner masked to the measurements taken by the other examiner.

The testing will be performed without cycloplegia and prior to the measurement of accommodative response using the Grand Seiko autorefractor. Accommodative response should be measured in the right eye three times using MEM retinoscopy and three times using Nott retinoscopy. For a given patient, the procedure (MEM or Nott retinoscopy) to be performed first will be randomized. The randomly-assigned testing order for each patient will be specified on a log sheet which the Coordinating Center will generate for each site.

The protocols for MEM and Nott testing are described in the Testing Procedures Manual.

CHAPTER 6: SAMPLE SIZE AND STATISTICAL ANALYSIS

The estimation of sample size and statistical analysis plan are summarized below and detailed in separate documents.

6.1 Sample Size Estimation

6.1.1 Randomized Trial

The sample size for the randomized trial has been estimated to be 50 patients per treatment group in order to have 90% power to detect at least a 0.60 D difference in myopia progression between treatment groups allowing for 10% loss to follow up. An adjustment for treatment group crossover was not made as this was very infrequent in COMET (2 out of 469 children) and is expected to be similarly infrequent in COMET2.

6.1.2 MEM and Nott Accommodation Ancillary Study

The sample size for the ancillary study has been estimated to be 300 patients. This sample size is based on the number of patients needed to have 0.05 half-widths for 95% confidence intervals for point estimates of sensitivities and specificities of 90%.

6.2 Statistical Analysis

6.2.1 Randomized Trial

6.2.1.1 Primary Analysis

The primary analysis will be a comparison of the average change from baseline to 3 years in amount of myopia between children in the single-vision lens group and the children in the progressive-addition lens group.

The primary outcome is change from baseline to 3 years in spherical equivalent refractive error (SER) in diopters (D) as measured by cycloplegic autorefraction. For each eye, the Grand Seiko autorefractor will yield 5 readings consisting of sphere, cylinder, and axis. Each reading will be converted to a spherical equivalent refractive error (SER) and the median of the 5 SER values will be used for analysis.

The primary analysis will be a treatment group comparison of mean 3-year change in amount of myopia using the t-test. For each time point, the spherical equivalent refractive error (SER) values for a given child will be calculated using the average of the spherical equivalent refractive errors from each eye. Change in amount of myopia will be calculated as the difference of the child's SER at 3 years minus the child's SER at baseline.

6.2.1.2 Secondary Analyses

Treatment effect will be assessed within subgroups based on the following factors: age, gender, ethnicity, prior spectacle wear, phoria, baseline refractive error, and accommodative lag.

Compliance with spectacle wear will be compared between treatment groups using a qualitative estimate of how often during waking hours the spectacles are worn.

Point estimates of change in myopia will be obtained for each treatment group from baseline to 1, 2 and 3 years and 95% confidence intervals calculated. Estimates of change between successive visits and 95% confidence intervals also will be calculated.

Point estimates and 95% confidence intervals for change in accommodative response will be calculated at 1 year, 2 years, and 3 years for each treatment group and change in accommodative response will be compared between treatment groups using t-tests.

6.2.1.3 Interim Analyses

Given the expected duration of recruitment (approximately 16 months), it is not possible that significant differences in SER at the primary outcome time (3 years) will be observed prior to the end of recruitment. Based on the effect size for children meeting COMET2 criteria seen in COMET, it also is unlikely that significant differences in the 3 year outcome will be observed prior to most or all children reaching the 3 year follow-up visit. Although interim significant differences at earlier follow-up times are possible, these may not be sustained through longer follow-up and would not constitute a reason to stop recruitment or follow-up in the study. Hence, a formal statistical monitoring plan for the primary outcome is not planned. However, an efficacy and safety report will be provided to the DSMC twice each year.

6.2.2 MEM and Nott Accommodation Ancillary Study

Data analysis will consist of determining the sensitivity and specificity for MEM and Nott testing methods. The Grand Seiko measurements of accommodative response will be considered the gold standard. Sensitivity and specificity will be based on the ability of MEM and Nott testing to properly classify patients as to whether reduced accommodative response is present.

95% confidence intervals will be calculated for both sensitivity and specificity for each testing method.

CHAPTER 7: REFERENCES

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