STUDY OF ADULT STRABISMUS (SAS1)

A Prospective Observational Study of Adult Strabismus

SAS1a: A Prospective Observational Study of Adult Convergence Insufficiency (CI)

SAS1b: A Prospective Observational Study of Adult Divergence Insufficiency (DI)

SAS1c: A Prospective Observational Study of Adult Small-Angle Hypertropia (HT)

PROTOCOL

Version 2.0
April 11, 2016

A PROSPECTIVE OBSERVATIONAL STUDY OF ADULT STRABISMUS (SAS1)

PROTOCOL AMENDMENT I (4-11-16)

Proposed Change #1

Current Protocol

- Enrollment visit: Questionnaires and the symptom survey (if applicable) should be administered to the subject prior to other examination procedures.
- Follow-up visits: No specific mention regarding order of testing with respect to questionnaires and the symptom survey.

Proposed Change

- Enrollment visit: Remove specific language regarding order of testing to allow questionnaires and the symptom survey (if applicable) to be completed at any time during the enrollment visit.
- Follow-up visits: Add specific language regarding order of testing at follow-up visits to require questionnaires and the symptom survey (if applicable) to be completed prior to testing.

Rationale for Change

At the time of enrollment, treatment has not yet been initiated, therefore having knowledge of clinical assessments prior to completion of the questionnaires and the symptom survey is not expected to introduce any bias. In contrast, the questionnaires and symptom survey should be completed prior to clinical testing at any follow-up visit.

Proposed Change #2

Current Protocol – For subjects enrolled with Divergence Insufficiency

Distance esodeviation of 2 PD to 30 PD and at least 50% greater than at near by PACT

Proposed Change – For subjects enrolled with Divergence Insufficiency

Distance esodeviation of 2 PD to 30 PD and distance deviation is at least 1.25 times (25% larger than) near deviation by PACT (i.e., maximum near deviation is at least 20% smaller than distance deviation). The distance deviation must exceed the near deviation by at least the amounts provided in the table below.

PACT Values for DI Eligibility

Distance Deviation	2	3	4	5	6	7	8	9	10	12	14	16	18	20	25	30
***Max Near Deviation**	1	2	3	4	4	5	6	7	8	9	10	12	14	16	20	20

Calculation: Distance ≥ Near x 1.25 or Near ≤ Distance x 0.8

*Near deviation is the nearest study-permitted prism based on Strabismus Procedures Manual.

Rationale for Change

The previous DI definition was developed by the SAS1 Planning Committee after literature review and chart reviews. After the study started, the Strabismus Steering Committee has lowered the threshold based on feedback from SAS1 investigators.

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CHAPTER 1: BACKGROUND AND SUMMARY

This study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG) and is funded through a cooperative agreement from the National Eye Institute.

1.1 Background

Epidemiology and clinical characteristics:

New onset adult strabismus has been estimated to affect 54.1/100,000 in a recent population-based study in the USA.[1] In this study, the most common types of new onset strabismus in adults, after paralytic strabismus, were convergence insufficiency (8.4/100,000), small angle hypertropia (7.5/100,000) and divergence insufficiency (6.0/100,000). For each of these types the incidence increased with increasing age.[1]

Convergence insufficiency:

Convergence insufficiency (CI) is characterized by an exodeviation greater at near than at distance and a remote near point of convergence and/or decreased positive fusional vergence.[2] It is typically associated with symptoms such as diplopia, eyestrain, asthenopia, frontal headaches or problems reading.[2-4] Treatment consists of either exercises,[3, 4] prisms,[3, 4] surgery,[4-6] or botulinum toxin injection.[7]

There is a paucity of evidence for the effectiveness of treatment for CI in adults, with most previous reports studying effects in children. A recent Cochrane review[2] identified two previous randomized clinical trials in adults. Teitelbaum et al[8] randomly assigned 29 presbyopic patients with symptomatic CI to either progressive addition lenses with base-in prism or progressive addition lenses with no prism. The authors concluded that base-in prism glasses were effective in reducing the symptoms of CI, although interestingly, symptoms also significantly improved with progressive addition lenses with no prism.[8] Birnbaum et al[9] randomly assigned 60 male adult patients to receive office-based vision therapy/orthoptics with supplemental home therapy, home vision therapy alone, or no treatment. Office vision therapy with supplemental home therapy was reported to be most effective with a success rate of 62%. Despite the findings of these two randomized trials there remains much uncertainty as to which treatments are most effective for a given adult patient with CI and what are realistic success rates.

Divergence insufficiency:

Divergence insufficiency (DI) esotropia is a comitant esodeviation worse at distance fixation than at near, typically associated with symptoms of diplopia at distance.[10] Treatment most often consists of either prism correction[10-13] or strabismus surgery.[14, 15] The established surgical procedure for DI esotropia is lateral rectus resection.[16-18] Nevertheless, in recent years bilateral medial rectus recession has been advocated.[14, 15, 19] There are few studies comparing treatments for DI esotropia, and little data on treatment outcomes, especially over the long-term. One recent study[19] claimed medial rectus recession was equivalent to lateral rectus resection but it was retrospective, not randomized, and had small sample size (n=24) and therefore of insufficient power to make such a determination.

Hypertropia:

New onset small angle hypertropia (HT) in adults presents as a comitant hyperdeviation, typically less than 10 prism diopters, in the absence of oblique muscle dysfunction. The patient

typically experiences symptoms of vertical diplopia. There are a range of possible causes for such vertical misalignment including skew deviation, sagging eye syndrome,[20] myotoxicity following cataract surgery,[21, 22] presumed micro-vascular event, or even central peripheral rivalry (dragged fovea-diplopia syndrome).[23-25] Treatment most often consists of prism correction of diplopia or strabismus surgery, although partial occlusion may be used in cases of central peripheral rivalry. Regarding surgical approaches for small angle HT, some surgeons perform superior rectus recession, while others have advocated mini-tenotomy (snip) procedures.[26] There are, however, limited data on the effectiveness of these treatments for small angle HT and few studies, if any, comparing treatment outcomes.

Prospective Observational Studies:

A prospective observational study monitors different forms of treatment applied to patients with a certain condition. Individuals are enrolled in a prospective observational study on the basis of either disease or exposure status. The care provider, not a protocol, decides how a patient gets treated. Through direct data collection from care providers, the results of the ongoing disease process and medical care can then be observed.

Prospective observational studies have the advantage of applying inclusion/exclusion criteria and not dictating management. The large patient sample often enables better estimation of outcome rates. Also, since data are collected within standard clinical practice, the results have high external validity. Weaknesses of observational studies include difficulty in identifying and controlling all sources of bias, and challenges with respect to data analyses. There may also be variability in time intervals between visits and treatments, and the potential for confounding makes treatment group comparisons difficult to interpret. Despite these weaknesses, future randomized controlled trials may be developed based on preliminary estimates of treatment effects that an observational study provides for the studied conditions.

1.2 Rationale for the study

Purpose of an adult CI-DI-HT strabismus prospective observational study:

A prospective adult strabismus observational study will provide data on the numbers, types and clinical characteristics of adult patients with CI, DI or HT who are seen by PEDIG investigators and are receiving certain types of treatments , and on the outcomes of those treatments over one year. These data will be used to generate hypotheses for possible future PEDIG studies, including randomized trials. Data collected will include angle of deviation, diplopia severity, treatment type, and treatment outcome.

Public health importance:

There are limited prospective, standardized data available on adults with convergence insufficiency, divergence insufficiency or small angle hypertropia, the commonest causes of non-paralytic adult strabismus. This study will inform regarding the numbers and types of adults with these conditions seen by PEDIG investigators, enabling the generation of hypotheses for potential PEDIG studies and estimation of their recruitment feasibility.

1.3 Considerations

It is recognized that estimates of treatment success may be biased by patient selection, but for some conditions / treatments, these data will be the best available for planning future PEDIG studies.

1.4 Study Objectives

To describe clinical characteristics, treatments, and one-year outcomes of adults with convergence insufficiency, divergence insufficiency, or small angle hypertropia. Treatment comparisons within the studied conditions will also be done to help develop future studies.

1.5 Synopsis of Study Design

1.5.1 Synopsis of Study Design for CI

Major Eligibility Criteria (*see section 2.2.1 for full details*)

- Adults ≥18 years of age (adult onset of CI not required)
- No strabismus surgery in the past 10 years
- CI Symptom Survey score ≥21 points
- Near exodeviation of ≥4Δ and at least 4Δ larger than at distance by PACT
- Distance exodeviation ≤15Δ by PACT
- Vertical deviation ≤2Δ at distance and near by PACT
- No constant exotropia at distance or near
- Reduced positive fusional vergence (PFV) at near (<20Δ or fails Sheard's criterion that the PFV measures less than twice the magnitude of the near phoria)
- Near point of convergence (NPC) of ≥6 cm break
- No paralytic strabismus, paretic strabismus, restrictive strabismus, monocular diplopia, thyroid eye disease, myasthenia gravis, chronic progressive external ophthalmoplegia, or eye movement abnormalities associated with known neurological disease. Patients with Parkinson's disease can be enrolled if non-paretic deviation.
- Visual acuity 20/50 or better in both eyes by ETDRS or Snellen
- Ability to fuse with prism in space *(see section 2.4.1)*
- Investigator is initiating treatment with prism, orthoptic exercises, botulinum toxin injection or surgery
- If initiating treatment with botulinum toxin or surgery, planned injection or surgery to be within 60 days of enrollment.
- Treatment to be initiated has not been used within the past one year

Treatment

Treatment is per the investigator's usual clinical practice.

Data will be collected for the following treatment modalities:

- Bilateral medial rectus muscle resection surgery
- Single medial rectus muscle resection surgery
- Recess lateral rectus muscle resection medial rectus muscle surgery
- Bilateral lateral rectus muscle recession surgery
- Single lateral rectus muscle recession surgery
- Botulinum toxin injection
- Prisms
- Orthoptic exercises, including computer-based therapy

Sample Size

50 subjects per non-surgical treatment modality (prism, orthoptic exercises) and up to 100 subjects undergoing surgery (maximum 50 per surgical modality) will be enrolled, for a total of

up to 200 subjects with CI. Recruitment will continue for 1 year, at which time the determination will be made whether the recruitment period should be extended to allow for additional subjects to be enrolled in treatment modality groups that have not reached their maximum.

Visit Schedule

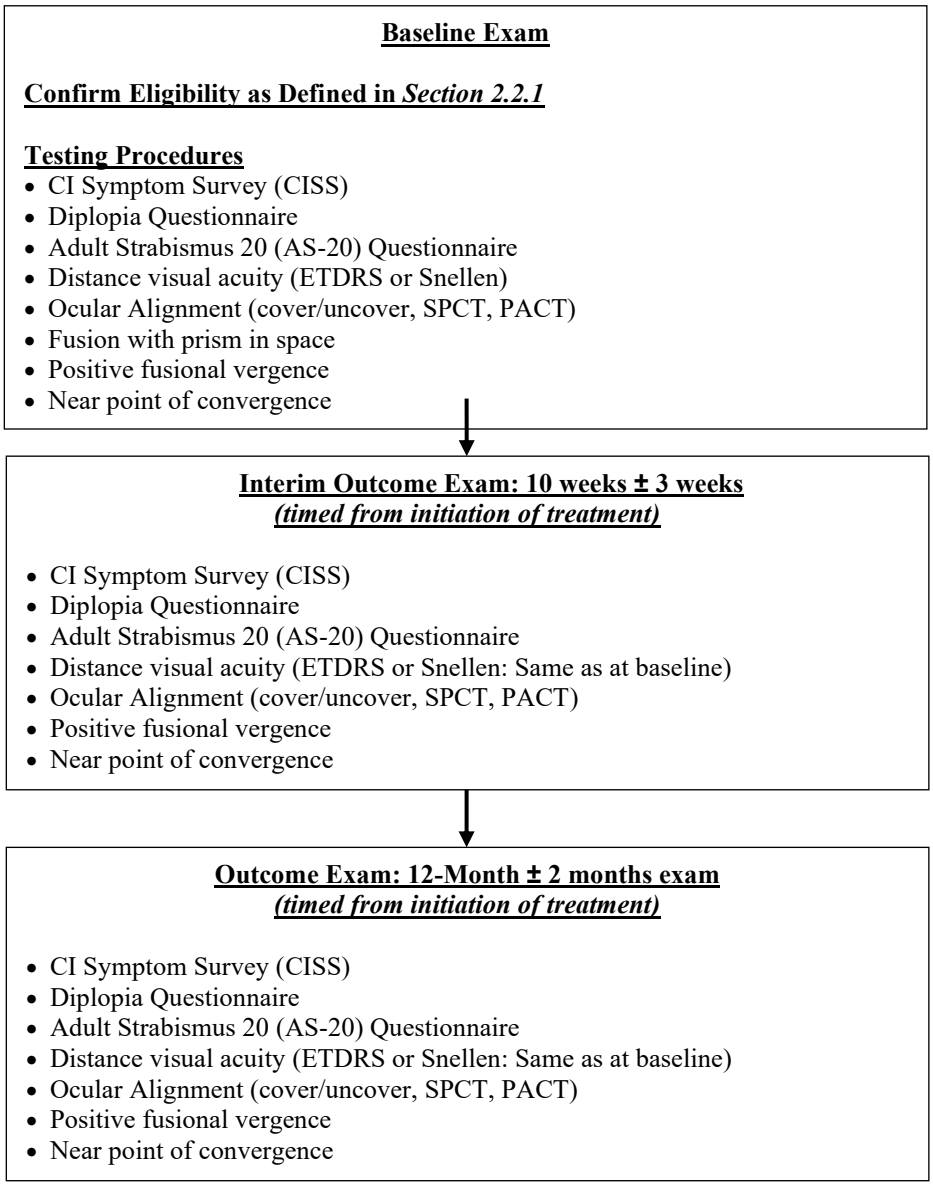
- Baseline Visit
- 10 week ± 3 weeks following intervention
- 12-months ± 2 months following intervention

Visits will be timed from the date of surgery or botulinum toxin injection (if applicable); or if prescribed prism or orthoptic exercises, visits will be timed from the day of enrollment. Subjects can remain in the study up to an additional year and have up to two additional follow up visits if their treatment modality is changed during the study.

Outcome

The primary outcome will be symptom success at the 10-week and 12-month visit, defined as improvement of CI Symptom Survey (CISS) score of at least 9 points and an outcome score of <21 points. For surgical treatment, a secondary, motor outcome will evaluate how often subjects have become orthotropic at distance and near after treatment.

1.5.2 Study Flow Chart: CI



1.5.3 Synopsis of Study Design for DI

Major Eligibility Criteria (*see section 2.2.2 for full details*)

- Adults ≥18 years of age
- Adult-onset DI (at ≥18 years of age)
- No prior strabismus surgery
- Symptoms of diplopia at distance with a frequency of sometimes or worse in primary position
- Distance esodeviation of 2Δ to 30Δ and distance deviation is at least 1.25 times (25% larger than) near deviation by PACT (i.e., maximum near deviation is at least 20% smaller than distance deviation). The distance deviation must exceed the near deviation by at least the amounts provided in the table below.

PACT Values for DI Eligibility

Distance Deviation	2	3	4	5	6	7	8	9	10	12	14	16	18	20	25	30
***Max Near Deviation**	1	2	3	4	4	5	6	7	8	9	10	12	14	16	20	20

Calculation: Distance ≥ Near x 1.25 or Near ≤ Distance x 0.8

*Near deviation is the nearest study-permitted prism based on Strabismus Procedures Manual.

- No more than 5Δ difference between right and left gaze by PACT
- No more than 10Δ difference between primary position and either upgaze or downgaze by PACT
- Any coexisting vertical deviation must be less than the distance esodeviation and ≤10Δ by PACT
- No paralytic strabismus, paretic strabismus, restrictive strabismus, monocular diplopia, thyroid eye disease, myasthenia gravis, chronic progressive external ophthalmoplegia, or eye movement abnormalities associated with known neurological disease. Patients with Parkinson's disease can be enrolled if non-paretic deviation
- Visual acuity 20/50 or better in both eyes by ETDRS or Snellen
- Ability to fuse with prism in space (*see section 2.4.2)*
- Investigator is initiating treatment with prism, orthoptic exercises, botulinum toxin injection, or surgery
- If initiating treatment with botulinum toxin or surgery, planned injection or surgery to be within 60 days of enrollment.
- Treatment to be initiated has not been used within the past one year

Treatment

Treatment is per the investigator's usual clinical practice.

Data will be collected for the following treatment modalities:

- Bilateral lateral rectus muscle resection surgery
- Single lateral rectus muscle resection surgery
- Recess medial rectus muscle resection lateral rectus muscle surgery
- Bilateral medial rectus muscle recession surgery
- Single medial rectus muscle recession surgery
- Botulinum toxin injection

- Prisms
- Orthoptic exercises, including computer-based therapy

Sample Size

50 subjects per non-surgical treatment modality (prism, orthoptic exercises) and up to 150 subjects undergoing surgery (maximum 50 per surgical modality) will be enrolled, for a total of up to 250 subjects with DI. Recruitment will continue for 1 year, at which time the determination will be made whether the recruitment period should be extended to allow for additional subjects to be enrolled in treatment modality groups that have not reached their maximum.

Visit Schedule

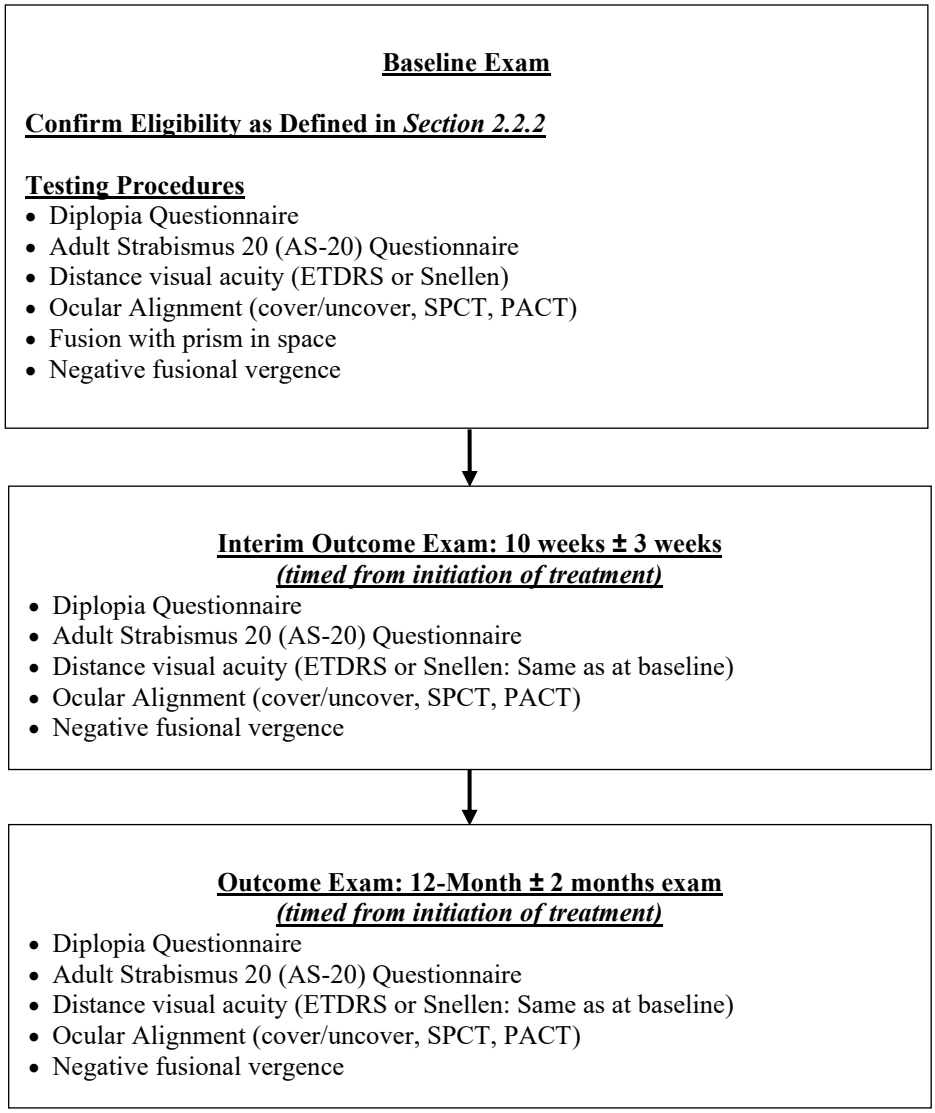
- Baseline Visit
- 10 week ± 3 weeks following intervention
- 12-months ± 2 months following intervention

Visits will be timed from the date of surgery or botulinum toxin (if applicable); or if prescribed prism or orthoptic exercises, visits will be timed from the day of enrollment. Subjects can remain in the study up to an additional year and have up to two additional follow up visits if their treatment modality is changed during the study.

Outcomes

The primary outcome will be symptom success at the 10-week and 12-month visit, defined as diplopia "rarely" or "never" in primary position at distance on the diplopia questionnaire. For surgical treatment, a secondary, motor outcome will evaluate how often subjects have become orthotropic at distance and near after treatment.

1.5.4 Study Flow Chart: DI



1.5.5 Synopsis of Study Design for HT

Major Eligibility Criteria (*see section 2.2.3 for full details*)

- Adults ≥18 years of age
- Adult-onset HT (at ≥18 years of age)
- No prior strabismus surgery
- Symptoms of diplopia at distance or near with a frequency of sometimes or worse in primary position at distance or reading position
- Vertical deviation ≥1Δ to ≤10Δ at distance and near by prism and alternate cover test (PACT)
- No more than 4Δ difference from the primary in any gaze position by PACT
- Any coexisting esodeviation must be less than the vertical deviation by PACT
- Any coexisting exodeviation ≤10Δ by PACT
- No convergence insufficiency as defined in *section 2.2.1*
- No paralytic strabismus, paretic strabismus, restrictive strabismus, monocular diplopia, thyroid eye disease, myasthenia gravis, chronic progressive external ophthalmoplegia, or eye movement abnormalities associated with known neurological disease. Patients with Parkinson's disease can be enrolled if non-paretic deviation
- Visual acuity 20/50 or better in both eyes by ETDRS or Snellen
- Ability to fuse with prism in space (*see section 2.4.3)*
- Investigator is initiating treatment with prism, orthoptic exercises, botulinum toxin injection or surgery
- If initiating treatment with botulinum toxin or surgery, planned injection or surgery to be within 60 days of enrollment.
- Treatment to be initiated has not been used within the past one year

Treatment

Treatment is per the investigator's usual clinical practice.

Data will be collected for the following treatment modalities:

- Vertical rectus muscle recession surgery
- Vertical rectus muscle mini-tenotomy (snip) surgery
- Botulinum toxin injection
- Prisms
- Orthoptic exercises, including computer-based therapy

Sample Size

50 subjects per non-surgical treatment modality (prism, orthoptic exercises) and up to 100 subjects undergoing surgery (maximum 50 per surgical modality) will be enrolled, for a total of up to 200 subjects with HT. Recruitment will continue for 1 year, at which time the determination will be made whether the recruitment period should be extended to allow for additional subjects to be enrolled in treatment modality groups that have not reached their maximum.

Visit Schedule

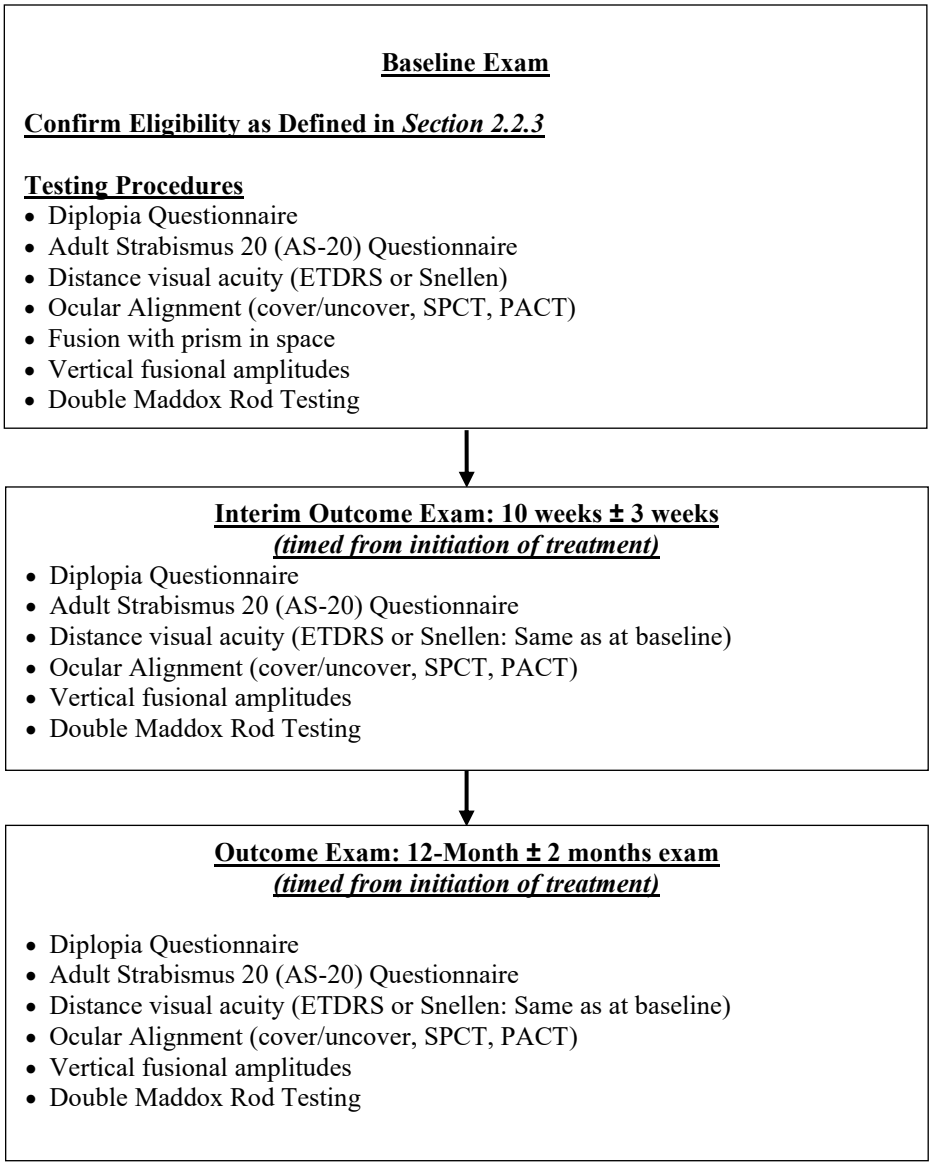
- Baseline Visit
- 10-week ± 3 weeks following intervention
- 12-months ± 2 months following intervention

Visits will be timed from the date of surgery or botulinum toxin injection (if applicable); or if prescribed prism or orthoptic exercises, visits will be timed from the day of enrollment. Subjects can remain in the study up to an additional year and have up to two additional follow up visits if their treatment modality is changed during the study.

Outcomes

The primary outcome will be symptom success at the 10-week and 12-month visit, defined as diplopia "rarely" or "never" both in primary position at distance and in reading position on the diplopia questionnaire. For surgical treatment, a secondary, motor outcome will evaluate how often subjects have become orthotropic at distance and near after treatment.

1.5.6 Study Flow Chart: HT



CHAPTER 2: SUBJECT ENROLLMENT

2.1 Eligibility Assessment and Informed Consent

A maximum of 650 subjects will be enrolled in the study. A maximum of 50 subjects per treatment modality (prism, orthoptic exercises, surgery of a specific type) per condition (CI, DI, HT) will be enrolled, with up to 100 CI subjects treated with surgery, up to 150 DI subjects treated with surgery, and up to 100 HT subjects treated with surgery. Recruitment will continue for 1 year, at which time the determination will be made whether the recruitment period should be extended to allow for additional subjects to be enrolled in treatment modality groups that have not reached their maximum.

A subject is considered for the study after undergoing a routine eye examination (by a study investigator as part of standard of care), or a referral, that identifies CI, DI, or HT that appears to meet the eligibility criteria. The study will be discussed with the subject. Subjects who express an interest in the study will be given a copy of the informed consent form to read. Written informed consent must be obtained from the subject prior to performing any study-specific procedures that are not part of the subject's routine care.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility Criteria for CI

The following criteria must be met for the subject to be enrolled into the study:

- Adults ≥18 years of age (adult onset of CI not required)
- No strabismus surgery within the past 10 years
- CI Symptom Survey score ≥21 points
- Near exodeviation of ≥4Δ and at least 4Δ larger than at distance by PACT
- Distance exodeviation ≤15Δ by PACT
- Vertical deviation ≤2Δ at distance and near by PACT
- No constant exotropia at distance or near
- Reduced positive fusional vergence (PFV) at near (<20Δ or fails Sheard's criterion that the PFV measures less than twice the magnitude of the near phoria)
- Near point of convergence (NPC) of ≥6 cm break
- Visual acuity 20/50 or better in both eyes by ETDRS or Snellen
- No paralytic strabismus (e.g., 3rd, 4th, or 6th cranial nerve palsies, skew deviation, Duane syndrome)
- No restrictive strabismus (e.g., blowout fracture, thyroid eye disease, post scleral buckle, Brown syndrome)
- No monocular diplopia
- No paretic strabismus, thyroid eye disease, myasthenia gravis, chronic progressive external ophthalmoplegia, or eye movement abnormalities associated with known neurological disease. Patients with Parkinson's disease can be enrolled if non-paretic deviation.
- No inferior or superior oblique overaction defined as 2+ or greater
- Ability to fuse with prism in space (*see section 2.4.1)*
- Ability to understand and complete a survey
- Investigator is initiating treatment with prism, orthoptic exercises, botulinum toxin injection or surgery

- If initiating treatment with botulinum toxin or surgery, planned injection or surgery to be within 60 days of enrollment
- Single treatment modality is planned (e.g., no combined prism and orthoptic exercises)
- Treatment to be initiated has not been used within the past one year

2.2.2 Eligibility Criteria for DI

The following criteria must be met for the subject to be enrolled into the study:

- Adults ≥18 years of age
- Adult-onset DI (at ≥18 years of age)
- No prior strabismus surgery
- Symptoms of diplopia at distance with a frequency of sometimes or worse in primary position (in current glasses if wearing glasses)
- Distance esodeviation of 2Δ to 30Δ and distance deviation is at least 1.25 times (25% larger than) near deviation by PACT (i.e., maximum near deviation is at least 20% smaller than distance deviation). The distance deviation must exceed the near deviation by at least the amounts provided in the table below.

PACT Values for DI Eligibility

Distance Deviation	2	3	4	5	6	7	8	9	10	12	14	16	18	20	25	30
***Max Near Deviation**	1	2	3	4	4	5	6	7	8	9	10	12	14	16	20	20

Calculation: Distance ≥ Near x 1.25 or Near ≤ Distance x 0.8

*Near deviation is the nearest study-permitted prism based on Strabismus Procedures Manual.

- No more than 5Δ difference between right and left gaze by PACT
- No more than 10Δ difference between the primary position at distance and either upgaze or downgaze ≤10Δ by PACT
- Any coexisting vertical deviation must be less than distance esodeviation and ≤10Δ by PACT
- Visual acuity 20/50 or better in both eyes by ETDRS or Snellen
- No paralytic strabismus (e.g., 3rd, 4th, or 6th cranial nerve palsies, skew deviation, Duane syndrome)
- No restrictive strabismus (e.g., blowout fracture, thyroid eye disease, post scleral buckle, Brown syndrome)
- No monocular diplopia
- No paretic strabismus, thyroid eye disease, myasthenia gravis, chronic progressive external ophthalmoplegia, or eye movement abnormalities associated with known neurological disease. Patients with Parkinson's disease can be enrolled if non-paretic deviation
- No inferior or superior oblique overaction defined as 2+ or greater
- Ability to fuse with prism in space (*see section 2.4.2)*
- Ability to understand and complete a survey
- Investigator is initiating treatment with prism, orthoptic exercises, botulinum toxin injection or surgery
- If initiating treatment with botulinum toxin or surgery, planned injection or surgery to be within 60 days of enrollment
- Single treatment modality planned (e.g., no combined prism and orthoptic exercises)
- Treatment to be initiated has not been used within the past one year

2.2.3 Eligibility Criteria for HT

The following criteria must be met for the subject to be enrolled into the study:

- Adults ≥18 years of age
- Adult-onset HT (at ≥18 years of age)
- No prior strabismus surgery
- Symptoms of diplopia at distance or near with a frequency of sometimes or worse in primary or reading position (in current glasses if wearing glasses)
- Vertical deviation ≥1Δ to ≤10Δ at distance and near by PACT
- No more than 4Δ difference from the primary in any gaze position by PACT
- Any coexisting esodeviation must be less than the vertical deviation
- Any coexisting exodeviation ≤10Δ by PACT
- No convergence insufficiency as defined in *section 2.2.1*
- Visual acuity 20/50 or better in both eyes by ETDRS or Snellen
- No paralytic strabismus (e.g., 3rd, 4th, or 6th cranial nerve palsies, skew deviation, Duane syndrome)
- No restrictive strabismus (e.g., blowout fracture, thyroid eye disease, post scleral buckle, Brown syndrome)
- No monocular diplopia
- No paretic strabismus, thyroid eye disease, myasthenia gravis, chronic progressive external ophthalmoplegia, or eye movement abnormalities associated with known neurological disease. Patients with Parkinson's disease can be enrolled if non-paretic deviation.
- No inferior or superior oblique overaction defined as 2+ or greater
- Ability to fuse with prism in space (*see section 2.4.3)*
- Ability to understand and complete a survey
- Investigator is initiating treatment with prism, orthoptic exercises, botulinum toxin injection or surgery
- If initiating treatment with botulinum toxin or surgery, planned injection or surgery to be within 60 days of enrollment
- Single treatment modality planned (e.g., no combined prism and orthoptic exercises)
- Treatment to be initiated has not been used within the past one year

2.3 Historical Information

Historical information collected at enrollment will include the following:

- Presence of co-existing neurological conditions (e.g., Parkinson's, Progressive supranuclear palsy, basal ganglia disease, stroke, or intracranial tumor) and any treatment
- Presence of epiretinal membrane, age-related macular degeneration (dry or neovascular), or macular pathology (if known)
- Heart disease
- Diabetes
- Autoimmune disease (other than myasthenia gravis and thyroid eye disease)
- Previous treatment for strabismus (surgical and/or non-surgical)
- Other major medical problems (e.g., significant head trauma)

2.4 Procedures at the Enrollment Visit

All examination procedures must be tested before initiating planned treatment and within 7 days of enrollment. All examination procedures at enrollment are performed in the subject's current correction, if required, and without cycloplegia. Any subjects wearing pre-study prism correction will be measured in trial frames without prism (unless otherwise noted below). If new correction is prescribed on the day of testing, or if the subject forgot to bring his/her spectacles, then testing should be done in trial frames. Full details for each procedure are listed in the *Procedures Manual*.

2.4.1 Enrollment Procedures for CI

1. Convergence Insufficiency Symptom Survey (CISS)

2. Diplopia Questionnaire (DQ)

3. Adult Strabismus 20 (AS-20) Questionnaire

4. Distance Visual Acuity
   - Monocular distance visual acuity testing will be performed in each eye using ETDRS or Snellen optotypes.
   - If wearing ground-in prism correction, testing will be done wearing current correction with prism; if wearing Fresnel prism, testing will be done in trial frames without prism correction.

The following must be tested by an examiner who is a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.

5. Ocular Alignment Testing
   - Ocular alignment will be assessed by the cover/uncover test and by simultaneous prism and cover test (SPCT) in primary gaze position at distance (6 meters) and at near (1/3 meter).
   - Prism and alternate cover test (PACT) will be tested at distance (6 meters) and near (1/3 meter) in primary position.

6. Fusion with Prism in Space
   - Ability to fuse with prism in space will be determined by asking the subject to view a 20/50 single optotype at 6 meters while neutralizing the deviation with free prisms. Subjects should be asked if they can make the image single. Subjects who are unable to make the image single are ineligible.

7. Positive Fusional Vergence (PFV)
   - PFV will be measured with a horizontal prism bar and a hand-held fixation target (20/50 single optotype) at 40 cm. Blur, break, and recovery points will be recorded. If no blur point is detected, the PFV score will be the break point measurement.

8. Near Point of Convergence (NPC)
   - Break and recovery values will be measured.

2.4.2 Enrollment Procedures for DI

1. Diplopia Questionnaire

2. Adult Strabismus 20 (AS-20) Questionnaire

3. Distance Visual Acuity
   - Monocular distance visual acuity testing will be performed in each eye using ETDRS or Snellen optotypes.
   - If wearing ground-in prism correction, testing will be done wearing current correction with prism; if wearing Fresnel prism, testing will be done in trial frames without prism correction.

The following must be tested by an examiner who is a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.

4. Ocular Alignment Testing
   - Ocular alignment will be assessed by the cover/uncover test and by simultaneous prism and cover test (SPCT) in primary gaze position at distance (6 meters) and at near (1/3 meter).
   - Prism and alternate cover test (PACT) will be tested at distance (6 meters) and near (1/3 meter) in primary position.

5. Fusion with Prism in Space
   - Ability to fuse with prism will be determined by asking the subject to view a 20/50 single optotype at 6 meters, and using prism(s), determine if any combination allows the subject to have single vision. Subjects who are unable to make the image single are ineligible.

6. Negative Fusional Vergence (NFV)
   - NFV will be measured with a horizontal prism bar while the subject is viewing an accommodative target (20/50 single optotype) at 6 meters. Blur, break, and recovery points will be recorded. If no blur point is measured, the NFV score will be the break point measurement.

2.4.3 Enrollment Procedures for HT

1. Diplopia Questionnaire

2. Adult Strabismus 20 (AS-20) Questionnaire

3. Distance Visual Acuity
   - Monocular distance visual acuity testing will be performed in each eye using ETDRS or Snellen optotypes.
   - If wearing ground-in prism correction, testing will be done wearing current correction with prism; if wearing Fresnel prism, testing will be done in trial frames without prism correction.

The following must be tested by an examiner who is a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.

4. Ocular Alignment Testing
    - Ocular alignment will be assessed by the cover/uncover test and by simultaneous prism and cover test (SPCT) in primary gaze position at distance (6 meters) and at near (1/3 meter).
    - Prism and alternate cover test (PACT) will be tested at distance (6 meters) and near (1/3 meter) in primary position.

5. Fusion with Prism in Space
    - Ability to fuse with prism will be determined by asking the subject to view a 20/50 single optotype at 6 meters, and using prism(s), determine if any combination allows the subject to have single vision. Subjects who are unable to make the image single are ineligible.

6. Vertical Fusional Amplitudes
    - Vertical fusional amplitudes will be measured with a vertical prism bar while the subject is viewing an accommodative target (20/50 single optotype) at 6 meters. Break and recovery points will be recorded. Measurements will be taken in both vertical directions to measure the range of vertical fusion.
    - Vertical deviation should be corrected at least with sufficient prism to give the subject single vision either in current correction (if pre-study prism) or with prism correction in trial frames.

7. Double Maddox Rod Testing
    - Ocular cyclotorsion will be assessed by double Maddox rod in primary gaze position at near (1/3 meters).

CHAPTER 3: TREATMENT AND FOLLOW-UP

3.1 Treatment

Treatment is at investigator discretion and may be changed or discontinued at any time during the study. The type of treatment and other treatment details (e.g., magnitude of prism, amount of orthoptic exercises) will be recorded at the time of enrollment when the treatment is prescribed. For surgical subjects, the type and amount of surgery will be recorded. If an adjustable technique is used, the final location of the muscle and alignment after adjustment will be recorded. For those treated with botulinum toxin injection, the muscle(s) injected and dose will be recorded. The timing of surgical intervention after enrollment is at investigator discretion; however, the enrollment assessments must be redone if surgery is not done within 60 days.

Changing treatment within a modality (e.g., frequency, strength, intensity) has no impact on the subject's visit schedule. Switching to a different treatment or adding a second treatment to the initial treatment has implications for the subject's visit schedule (*see section 3.5*).

3.2 Visit Schedule

Subjects enrolled will have visits at the following times:

- 10 weeks ± 3 weeks following intervention
- 12 months ± 2 months following intervention

Visits will be timed from the date of surgery or botulinum toxin injection (if applicable); or if prescribed prism or orthoptic exercises, will be timed from the day of enrollment. If a new treatment is initiated, the visit schedule may restart or the subject's study participation may end, according to the details in *section 3.5*.

3.3 Follow-up Visit Testing Procedures (10-week and 12-month visits)

At each visit, data on treatments received, any change in the amount/intensity of treatment, or any major change in eye condition since the last visit will be collected. In addition, the following will be performed / completed as done at the enrollment exam in the subject's current correction, if required, and without cycloplegia. Questionnaires and the symptom survey (if applicable) should be administered to the subject prior to other examination procedures. Any subjects wearing prism correction will be measured in trial frames without prism (unless otherwise noted below). If new correction is prescribed on the day of testing, or if the subject forgot to bring his/her spectacles, then testing should be done in trial frames.

3.3.1 Follow-up Visit Testing Procedures for CI

See *section 2.4.1* for details.

1. CISS
2. Diplopia Questionnaire
3. AS-20 Questionnaire
4. Distance Visual Acuity
    - If wearing ground-in prism correction, testing will be done wearing current correction with prism; if wearing Fresnel prism, testing will be done in trial frames without prism correction.
5. Ocular Alignment Testing
6. Positive Fusional Vergence

7. Near Point of Convergence

3.3.2 Follow-up Visit Testing Procedures for DI

See *section 2.4.2* for details.

1. Diplopia Questionnaire
2. AS-20 Questionnaire
3. Distance Visual Acuity
   - If wearing ground-in prism correction, testing will be done wearing current correction with prism; if wearing Fresnel prism, testing will be done in trial frames without prism correction.
4. Ocular Alignment Testing
5. Negative Fusional Vergence

3.3.3 Follow-up Visit Testing Procedures for HT

See *section 2.4.3* for details.

1. Diplopia Questionnaire
2. AS-20 Questionnaire
3. Distance Visual Acuity
   - If wearing ground-in prism correction, testing will be done wearing current correction with prism; if wearing Fresnel prism, testing will be done in trial frames without prism correction.
4. Ocular Alignment Testing
5. Vertical Fusional Amplitudes
   - Vertical deviation should be corrected at least with sufficient prism to give the subject single vision either in current correction (if pre-study prism) or with prism correction in trial frames.
6. Double Maddox Rod Testing

3.4 Non-study Visits

Additional non-study visits and treatment are at investigator discretion. Investigators must follow the procedures for initiating a new treatment during the study as outlined in *section 3.5*.

3.5 Initiating a New Treatment

If any new treatment is initiated during the study an early outcome exam as outlined in *section 3.3* will be completed. Study participation will end if the new treatment is prism or exercises, unless initially enrolled in the surgery or botox injection group. If the new treatment is a new surgical modality or botox injection (not a re-operation or re-injection in the study), the examination will serve both as the outcome exam for the initial treatment and the baseline exam for the newly initiated surgery or botox injection, if the subject still meets eligibility criteria. The subject will then be followed for an additional 12-months in the study in the new treatment, as if they had been newly enrolled.

In the event that the study category for the newly initiated surgical modality is no longer recruiting subjects, the subject will complete an early outcome exam at the time the new surgery or botox injection is prescribed and study participation will end for this subject.

Subjects who have had surgery or botox injection as their initial treatment (or as a new treatment during the study) will continue to be followed until the 12-month outcome exam whether or not an additional treatment is initiated. The exception is if a re-operation or re-injection is planned prior to the 12-month outcome. In this case, an early outcome exam will be completed at the time surgery is prescribed. Study participation will end following the outcome examination.

Subjects who have completed the study and are returning for additional treatment following an unspecified period of time beyond the outcome exam may be enrolled a second time provided they meet eligibility criteria and the study category for the newly initiated treatment is still recruiting subjects. Subjects enrolling as a study subject a second time must repeat the consent process.

CHAPTER 4: MISCELLANEOUS CONSIDERATIONS

4.1 Contacts by the Jaeb Center for Health Research and Sites

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the subject's contact information. The Jaeb Center will contact each subject one month before any 12-month visit (including a second 12-month visit which could be required if the patient changed treatments during the study). Permission for such contacts will be included in the Informed Consent Form. The principal purpose of the contacts will be to help coordinate scheduling of the 12-month outcome examination.

4.2 Subject Withdrawals

Subjects may withdraw from the study at any time. This is expected to be a very infrequent occurrence in view of the study design's similarity to routine clinical practice. If the subject indicates they want to withdraw from the study, the investigator personally should attempt to speak with them to determine the reason. If their interest is in transferring their care to another eye care provider, every effort should be made to comply with this and at the same time try to keep the participant in the study under the new provider's care.

4.3 Management of Refractive Error

Management of refractive error is at the discretion of the investigator.

4.4 Risks

There are no risks in this study that would not be part of usual care.

4.4.1 Risks of Examination Procedures

The procedures in this study are part of daily eye care practice in the United States and pose no known risks.

4.5 Reporting of Adverse Events

No treatments are being prescribed that are not part of usual care. Investigators will abide by local IRB reporting requirements.

4.5.1 Risk Assessment

It is the investigators' opinion that the protocol's level of risk is research not involving greater than minimal risk.

4.6 Discontinuation of Study

The study may be discontinued by the Steering Committee (with approval of the Data and Safety Monitoring Committee) prior to the preplanned completion of enrollment and follow-up for all subjects.

4.7 Travel Reimbursement

Subjects will be compensated $25 for each 10-week visit and $50 for each 12-month visit (by money-card) up to a maximum of $150. If there are extenuating circumstances, and the subject

is unable to complete study visits without additional funds for travel costs, additional funds may be provided.

4.8 Study Costs

The study will pay for visits specific to the research study, but will not pay for usual care visits that would occur whether or not the subject was in the study. The cost of usual care visits will be the responsibility of the participant or his/her insurance company.

Any costs associated with treatment will not be paid for by the study and will be the responsibility of the participant or his/her insurance company.

4.9 General Considerations

The study is being conducted in compliance with the policies described in the network policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

Data will be directly collected in electronic case report forms, which will be considered the source data.

There is no restriction on the number of participants to be enrolled by a site. A risk-based monitoring approach will be followed, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013).

CHAPTER 5: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

5.1 Assessment of Investigator Interest / Recruitment Potential

At the February 2014 PEDIG Study Group meeting, 18 (44%) of 41 ophthalmologist investigators and 26 (65%) of 40 optometrists investigators indicated they would be willing to participate in this study. In addition, 8 (20%) of 41 ophthalmologists and 8 (20%) of 40 optometrists rated this protocol in the top 5 of 18 protocol ideas reviewed with the group. The study ranked 13th among the 18 protocol ideas reviewed with the group for the 81 investigators overall.

Table 1 shows a summary of the results from a February 2015 email survey of PEDIG investigators. For each condition (CI, DI, and HT), investigators were asked whether they treated patients with the condition and how many they treated with various treatment modalities over the course of one year.

Table 1: Assessment of Recruitment Potential

	Number of Patients Treated in One Year In PEDIG Network*		
Condition	**Prism**	**Orthoptic Exercises**	**Surgery**
CI	229	192	23**
DI	119	20	85***
HT	194	10	39****

* Cases treated with more than one type of treatment are counted for each type of treatment.
** Bilateral medial rectus resection (N=11), other (N=12)
*** Bilateral medial rectus recession (N=51), bilateral lateral rectus resection (N=13), other (N=21)
****Vertical rectus recession (N=37), other (N=2)

5.2 Sample Size

The maximum total sample size of 650 is based on a convenience sample of a maximum of 50 subjects per treatment modality (prism, orthoptic exercises, surgery of a specific type) per condition (CI, DI, HT), with up to 100 subjects treated with surgery for CI and for HT, and up to 150 subjects treated with surgery for DI (Table 2).

Table 2: Maximum Sample Size for Each Condition/ Treatment Modality

	Maximum Sample Size		
Condition	**Prism**	**Orthoptic Exercises**	**Surgery**
CI	50	50	100*
DI	50	50	150*
HT	50	50	100*

*Within this limit for the total number of surgeries for a given condition, no more than 50 surgeries of a specific type (e.g. bilateral medial rectus recessions, bilateral lateral rectus resection, botulinum toxin injection, etc.) may be enrolled.

Based on the assessment of recruitment potential (*section 5.1*), about half of the modality/condition groups would be expected to be filled to 50 subjects within one year (see Table 1). The remaining modality/condition groups might have a smaller-than-desired sample size for analysis or might require recruitment for more than one year.

Table 3 shows the expected half-widths for the 95% confidence interval for the success proportion estimate for each modality/condition group.

Table 3: Expected ½-Width of 95% Confidence Interval as a Function of Sample Size and Success Proportion*

One-Year Success Proportion	Sample Size				
	10	**20**	**30**	**40**	**50**
1%	6%	4%	4%	3%	3%
3%	11%	8%	6%	5%	5%
5%	14%	10%	8%	7%	6%
10%	19%	13%	11%	9%	8%
15%	22%	16%	13%	11%	10%
20%	25%	18%	14%	12%	11%
25%	27%	19%	16%	13%	12%
30%	28%	20%	16%	14%	13%
40%	30%	22%	18%	15%	14%
50%	31%	22%	18%	15%	14%

***Note**: The grey boxes indicate that validity of confidence interval widths is questionable because the normal approximation might not be valid given these low probability of success and/or small sample sizes.

After accounting for up to 5% loss to follow-up, a sample size of 50 patients per treatment modality (prism, orthoptic exercises, surgery of a specific type) per condition would contribute about 47 subjects to the point estimate for a dichotomous success/failure outcome at one year. With 47 subjects, the maximum width of the resulting confidence intervals on each point estimate would be ±14%.

5.3 Primary Analysis – Symptom Success at One Year

For each of the modality/condition groups, the primary analysis will be an estimation of the proportion of patients of patients with treatment success based on improvement of symptoms at 10 weeks post intervention and at one year, with 95% confidence intervals.

Table 4 shows the criteria for symptom success for each condition, which will be used to assess all treatment modalities.

Table 4: One-Year Symptom Success Criteria for Each Condition

Condition	One-Year Symptom Success Criteria
CI	improvement of CI Symptom Survey (CISS) score of at least 9 points AND a score of <21 points
DI	diplopia no more than rarely in the past week in the primary position (question #1.1 on the Diplopia questionnaire)
HT	diplopia no more than rarely in the past week both in the primary position and for reading (questions #1.1 and #1.2 on the Diplopia questionnaire)

For patients who initiate a new treatment before completing one year of follow-up, the symptom success/failure status from the visit at which treatment was changed (i.e., the 10-week interim visit or an early outcome visit) will be brought forward as their one-year outcome.

Rubin's multiple imputation[21] will be used to impute outcome for patients who have not changed treatments but who are who are lost to follow-up or withdraw from the study prior to one-year exam.

5.4 Secondary Analysis – Motor Success at One Year

For each surgery type within a condition, a secondary objective will be to calculate the proportion of patients with motor success at one year and a 95% confidence interval. Motor success will be defined as orthotropia by cover/uncover at distance and near fixation in primary position at one year. Similar to the primary analysis of symptom success, for patients who change treatments before completing one year of follow-up, the motor success/failure status from the visit at which treatment was changed (i.e., the 10-week interim visit or an early outcome visit) will be brought forward as the one-year outcome. In addition, Rubin's multiple imputation[21] will be used to impute outcome for patients who have not changed treatments but who are who are lost to follow-up or withdraw from the study prior to one-year exam.

5.5 Additional Analyses

5.5.1 Secondary Outcomes at One Year

Secondary outcomes at one year will be evaluated within each modality/condition. Secondary outcomes to be assessed include motor alignment, near point of convergence (CI only), positive fusional vergence (CI only), negative fusional vergence (DI only), vertical fusional vergence (HT only), and the Adult Strabismus 20 (AS-20) questionnaire. In addition, mean CI Symptom Survey (CISS) score will be evaluated for CI, and the AS-20 and Diplopia Questionnaire will be evaluated as a continuous outcomes for all three conditions.

5.5.2 Outcomes at 10 Weeks

Outcomes at the 10-week interim visit will be evaluated similarly to the primary and secondary analyses defined for one-year time points (*sections 5.3, 5.4 and 5.5.1*).

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