Chapter 1: Background and Study Organization

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1.1 CITT Specific Aims

The Convergence Insufficiency Treatment Trial (CITT) is a prospective, masked, placebo-controlled, multi-center clinical trial in which 208 subjects between the ages of 9 to < 18 years will be randomly assigned to: 1) Home-based Pencil Push-Up Therapy, 2) Home-based Pencil Push-ups with Computer Vision Therapy/Orthoptics, 3) Office-based Vision Therapy/Orthoptics, or 4) Placebo Office-based Vision Therapy/Orthoptics. Measurements of the signs and symptoms of CI will be made at the eligibility examination, and by masked examiners after 4, 8 and 12 weeks of treatment have been completed. Long term follow-up will be assessed at 6 and 12 months after the completion of active treatment.

The primary goal is to answer the following question:

After 12 weeks of treatment for CI, is Home-based Pencil Push-up therapy, Home-based Pencil Push-ups with Computer Vision Therapy/Orthoptics (VT/Orthoptics) or Office-based VT/Orthoptics more effective than placebo treatment (placebo VT/Orthoptics,) and is there a difference between the three treatments in improving subject symptoms and signs? We will test the null hypothesis that there is no difference in the outcome among the four treatment groups. If the null hypothesis is rejected, we will perform multiple comparisons between the groups to determine which differences in outcomes are significant.

The primary outcome measure is a symptom score obtained via the Convergence Insufficiency Symptom Survey. The secondary outcome measures are the near point of convergence and positive fusional vergence at near. These measures were tested and validated for this study by members of our study group under an NEI R21 Clinical Trial Planning Grant, and the CITT is powered at 90% to test differences across treatment arms for each of the outcome measures.

Effectiveness will be assessed by comparing the mean of each outcome measure (either CI Symptom Survey score, near point of convergence or positive fusional vergence) obtained at the 12-week masked examination between the four treatment groups. The results of all of these comparisons will then be synthesized into a final conclusion about the relative effectiveness of each treatment arm. If we are to conclude that Office-based VT/Orthoptics is a more effective treatment for CI than the other two treatments tested, results from our pair-wise comparisons must show that Office-based VT/Orthoptics was significantly different (and the mean indicative of a clinically-relevant improvement) than Office-based Placebo VT/Orthoptics and both of the other therapy arms. If, instead, we are to conclude that Home-based Pencil Push-ups with Computer VT/Orthoptics is the most effective, this group must be found to perform as well as or significantly better than Office-based VT/Orthoptics and significantly better (and the mean indicative of a clinically-relevant improvement) than either Home-based Pencil Push-up or Office-based Placebo VT/Orthoptics. Similarly, if Home-based Pencil Push-up therapy performs as well as or significantly better than the other three treatment groups (and the mean for Home-based Pencil Push-up therapy indicates clinically-relevant improvement), then our conclusion would be that Home-based Pencil Push-up therapy is the most effective treatment for CI.

Additional questions to be answered include:
1. What percentage of subjects in each treatment group would be classified as successful or improved after completion of 12 weeks of treatment? The definition of successful has 3 components: a) a symptom score <16, b) a near point of convergence <6 cm and c) normal positive fusional vergence at near (>15° and passes Sheard’s Criterion, i.e., positive fusional vergence is at least twice the phoria). Similarly the definition of improved has 3 components: a symptom score <16 or a change in symptom score from eligibility to 12-week of ≥10 points AND a) a near point of convergence <6 cm or a change from eligibility to 12-week of ≥4 cm OR b) normal positive fusional vergence at near or a change from eligibility to 12-week of ≥10°.

2. Are improvements in outcome measures still present at the 6-month and 12-month follow-up examinations for subjects who scored less than 16 on the Convergence Insufficiency Symptom Survey after 12 weeks of treatment?

3. Could shorter treatment durations provide similar effects?
   a. Were any treatment group differences observed at the 12-week outcome visit also present at the masked examinations after 4 and 8 weeks of treatment?
   b. Is there a significant improvement in the outcome measures between successive masked examinations for each of the treatment groups?

1.2 Background and Significance

1.2.1 Definition of CI

Convergence insufficiency (CI) has one or more of the following signs: 1) exophoria that is greater at near than at distance, 2) a remote near point of convergence (NPC), and 3) decreased positive fusional vergence (PFV) at near.¹⁻³

Some authors have defined CI using all three signs, while others use only one or two of these signs. The CITT Study Group is studying the condition in which all three signs are present. Members of our group have completed a preliminary study demonstrating the prevalence of CI based on this definition in a school-age population.

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Age Range (years)</th>
<th>N</th>
<th>CI Classification Criterion</th>
<th>CI Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letourneau et al. ¹¹(1979)</td>
<td>Elementary school</td>
<td>7-14</td>
<td>735</td>
<td>NPC &gt;10cm penlight target</td>
<td>8.3%</td>
</tr>
<tr>
<td>Letourneau et al. ¹²(1988)</td>
<td>Elementary school</td>
<td>6-13</td>
<td>2054</td>
<td>exophoria greater at near than distance NPC &gt;10cm</td>
<td>2.25%</td>
</tr>
<tr>
<td>Porcar and Martinez-Palomera ¹³(1997)</td>
<td>University students</td>
<td>19-25</td>
<td>65</td>
<td>&gt; 6° exophoria at near NPC less than normal PFV less than normal</td>
<td>7.7%</td>
</tr>
<tr>
<td>Rouse et al. ¹⁴(1999)</td>
<td>Elementary school</td>
<td>10-12</td>
<td>415</td>
<td>exophoria greater at near NPC &gt; 7.5 cm PFV &lt;12° blur or &lt;15° break or fails Sheard’s criteria</td>
<td>4.2%</td>
</tr>
</tbody>
</table>
1.2.2 Prevalence of CI

Review of the literature reveals considerable variability in the reported prevalence of CI ranging from 1.75 to 33%.\textsuperscript{2, 4-10} This variation may be accounted for by the different definitions used by the authors and by the different clinical samples studied. A more accurate estimate of the true prevalence of CI would be based on population-based studies. Four such studies\textsuperscript{11-14} narrow the range from 2.25% to 8.3% (Table 1-1). No supportive data could be found to indicate whether the prevalence of CI varies across ethnic and/or racial subgroups.

1.2.3 Impact of CI on Quality of Life

Common symptoms of CI include discomfort, eyestrain, headaches, blurred vision, diplopia, sleepiness, difficulty concentrating, movement of print, and loss of comprehension after short periods of time (Table 1-2).\textsuperscript{3,4,15-19} Most symptoms of CI are associated with reading or other close work. Therefore, CI may have a significant negative impact on quality of life, potentially interfering with school, work performance, and leisure activities. The CITT Study Group, therefore, decided that symptoms must be part of our definition of CI. However, none of the population-based studies included the presence of symptoms in their definitions of CI. Therefore, we developed a CI Symptom Survey which provides a symptom score that is used as a component in the diagnosis of CI and as the primary outcome measure for the CITT Pilot Study and for this full-scale CITT Study.

Although symptoms of CI are commonly reported in the literature, the CI Symptom Survey is the first standardized symptom tool for documenting the type and frequency of symptoms in CI subjects. Existing vision-specific quality of life measures have focused on visual acuity and the postoperative effects of surgery. Therefore, such measures are not appropriate for evaluating subjects with CI who have normal visual acuity and are expected to have difficulties with performing sustained visual activities within arm’s length.

<table>
<thead>
<tr>
<th>Study</th>
<th>Eyestrain or Burning</th>
<th>Headaches</th>
<th>Blur</th>
<th>Diplopia</th>
<th>Sleepiness</th>
<th>Difficulty Concentrating</th>
<th>Movement of print</th>
<th>Loss of Comprehension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirsch</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kent</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazow</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Duke-Elder</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pickwell</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daum</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Scheiman</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

The CITT study group, in preparation for its planning grant, performed a preliminary study to help address this issue. Borsting et al.\textsuperscript{20} gathered validity-related evidence on child and parent versions of the CI Symptom Survey. Symptoms were measured prospectively on 14 school-aged (8-13 years) children with CI and 14 children with normal binocular vision (controls). The two groups had similar characteristics for age, gender, and cognitive level; children with learning disabilities or attention deficit disorder were excluded from the study. The CI group scored significantly higher than the controls on both the child and parent surveys. Thus, CI appears to have a significant negative impact on children’s visual comfort.
The CI Symptom Survey was further refined and studied in the recently completed CITT Planning Grant. The new CI Symptom Survey form is illustrated in the Appendix located at the end of this chapter. This study demonstrated that the CI Symptom Survey has moderately good repeatability for individuals 9 to <18 years of age. The instrument also has the ability to differentiate between CI and normal binocular vision subjects.

Symptoms are usually the main reason patients with CI seek professional eye care. Thus, an important eligibility criterion for this trial will be that the CI patient must demonstrate a significant level of symptoms i.e., a CI Symptom Survey score of ≥16. Because reduction of symptoms is the primary goal of subjects who seek care, the score on the CI Symptom Survey will also be the primary outcome measure for our study.

1.2.4 Treatment Options

1.2.4.1 Review of the Literature

A review of the literature suggests that some form of “active” convergence therapy is the treatment of choice, however, there is no consensus about the therapy procedures to be prescribed or whether the treatment should be home- or office-based (Table 1-3).

<table>
<thead>
<tr>
<th>Source</th>
<th>Author</th>
<th>Key Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binocular Vision and Ocular Motility</td>
<td>von Noorden</td>
<td>“Therapy for convergence insufficiency is in the realm of orthoptics. Indeed its treatment is one of the most successful applications of the art of orthoptics…”</td>
</tr>
<tr>
<td>Duke-Elder’s Practice of Refraction</td>
<td>Abrams</td>
<td>In reference to convergence insufficiency - “Orthoptic training appears at its best in the treatment of this condition…”</td>
</tr>
<tr>
<td>Pediatric Ophthalmology</td>
<td>Cibis, Tongue and Stass-Isern</td>
<td>“Most convergence insufficiency subjects can be cured or relieved of their symptoms with appropriate exercises”.</td>
</tr>
<tr>
<td>Management of Strabismus and Amblyopia</td>
<td>Pratt-Johnson</td>
<td>“Orthoptics is the treatment of choice in most subjects with convergence insufficiency and gives excellent results.”</td>
</tr>
<tr>
<td>Strabismus; A Decision Making Approach</td>
<td>von Noorden and Helveston</td>
<td>In reference to convergence insufficiency - “The treatment, orthoptic exercises, in most instances provides long-lasting relief from symptoms.”</td>
</tr>
<tr>
<td>Binocular Anomalies: Diagnosis and Vision Therapy</td>
<td>Griffin and Grisham</td>
<td>“…vision therapy is the preferred option applied in these cases.”</td>
</tr>
<tr>
<td>Applied Concepts in Vision Therapy</td>
<td>Press</td>
<td>“Convergence insufficiency is the condition most responsive to vision therapy.”</td>
</tr>
<tr>
<td>Clinical Management of Binocular Vision</td>
<td>Scheiman and Wick</td>
<td>“Vision therapy is the treatment of choice for convergence insufficiency.”</td>
</tr>
</tbody>
</table>
1.2.4.2 National Survey of Optometrists and Ophthalmologists

Two studies have surveyed the ophthalmic community to determine how CI is treated in routine clinical practice. Chin et al. \textsuperscript{30} surveyed 300 optometrists in the San Francisco Bay area regarding their primary mode of treatment for CI. One hundred six optometrists responded. The two most commonly recommended treatments were pencil push-up therapy (34\%) and vision therapy/orthoptics (22\%). About 20\% prescribed base-in prism, 18\% referred to another practitioner, and 6\% did not recommend any treatment.

As part of our planning process we completed a similar survey to determine treatment patterns for CI patients using a randomly selected national sample of 863 optometrists and 863 ophthalmologists.\textsuperscript{31} Fifty-eight percent of the optometrists (563) and 23\% of the ophthalmologists (196) responded to the survey. Among optometrists, 36\% recommended pencil push-ups, 22\% recommended more extensive home-based vision therapy, 16\% prescribed office-based vision therapy/orthoptics, 15\% prescribed base-in prism glasses, and 3\% did not recommend any treatment for symptomatic CI subjects. Although only 16\% of the respondents reported that they prescribed office-based vision therapy/orthoptics, 69\% felt that this treatment approach was at least as effective as the other approaches included in the survey. Among ophthalmologists, 50\% recommended pencil push-up therapy, 21\% recommended more extensive home-based vision therapy/orthoptics, 5\% prescribed vision therapy/orthoptics, 28\% prescribed base-in prism glasses, and 8\% did not recommend any treatment. In contrast to optometrists, only 4\% of the respondents felt that vision therapy/orthoptics was at least as effective as the other approaches. These surveys underscore the lack of consensus among eye care professionals regarding the most appropriate treatment for CI and emphasize the need for a clinical trial.

Two very different “active” convergence treatments are commonly prescribed: 1) home-based or pencil push-up therapy and 2) office-based vision therapy/orthoptics. Pencil push-up therapy is the most commonly prescribed treatment and, therefore, is the current standard of care. This form of treatment involves home-based therapy with no specialized equipment and little or no follow-up. On the other hand, office-based vision therapy/orthoptics involves weekly office visits and a considerable number of therapy procedures and equipment.

1.2.4.3 Home-based Pencil Push-Up Treatment for CI

Many eye care practitioners responded that they believed pencil push-up therapy is an effective treatment procedure for CI and that pencil push-up therapy was the most frequently prescribed treatment.

The basic pencil push-up technique is described in Duke-Elder.\textsuperscript{17} "Exercises to improve the near point of convergence are carried out simply by the subject holding a target at arm's length and then gradually bringing it towards the eye, all the time maintaining bifoveal fixation. These exercises should be carried out several times each day for a few minutes." Use of a target providing physiological diplopia is often recommended.\textsuperscript{22, 28, 29, 32}
Even so, there is only one reported clinical study investigating the efficacy of pencil push-up therapy. In that uncontrolled study, 25 subjects with symptomatic CI between 9 and 51 years of age (mean age 25 years) were instructed to perform pencil push-up therapy at home for 15 minutes, 5 days a week, and to fill out a daily log. Symptoms were significantly improved for the group of 12 subjects who returned for the 6-week follow-up visit. Both objective findings and symptoms were improved for seven subjects, while five subjects showed no improvements.

Our CITT Planning Project is the only controlled study of the efficacy of pencil push-up therapy. Significant improvements were not found with pencil push-up therapy in subjects aged 9 to 18 years. In the Pencil Push-up group there was neither a statistically nor clinically significant change in the symptom score (29.3±5.4 to 25.9±7.3, p=0.24). There was a moderate improvement in near point of convergence for subjects assigned to the Pencil Push-ups group (14.6cm ±7.4 to 9.1cm ±5.1, p=0.08). Only 27.3% (3/11) of the subjects achieved a normal near point of convergence break measurement of less than 6 cm at the end of treatment. The positive fusional vergence break showed no statistically significant improvement (12.6Δ ±3.2 to 14.5Δ ±5.3, p=0.22).

Although there is a lack of scientific support for pencil push-up therapy, it is easy to understand the clinical popularity of this technique because of its simplicity and low cost. Standard, home-based pencil push-up therapy can be taught to the subject and prescribed in a very short period of time. It also requires no or few follow-up visits and no specialized equipment. Therefore, it is significantly less expensive and time consuming for the subject. Consequently, pencil push-up therapy should be the treatment of choice for CI if it is as effective as or more effective than office-based vision therapy/orthoptics.

1.2.4.4 Home-Based Pencil Push-ups with Computer Vision Therapy/Orthoptics for CI

Our survey indicated that about 24% of ophthalmologists and almost 36% of optometrists fairly often, often, or always recommend home-based therapy that is more intensive than just standard pencil push-ups. In the survey, home-based vision therapy/orthoptics (VT/orthoptics) was described as the use of prism, stereoscopes or any other home-based device. The use of computer technology in vision therapy started to become a reality in the 1980s, and has become an important part of vision therapy/orthoptics in the past 10 years.

There are several disadvantages of traditional home-based vision therapy/orthoptics including:

1. Traditional techniques often require an experienced doctor/technician to interpret the patients' responses and to use that information to alter stimulus conditions in order to improve binocular response.
2. With children who are not responding accurately for a variety of reasons, traditional techniques become difficult and unreliable to use. The child who "learns" the expected response and has a strong desire to please the therapist may "give the right response" even though he is not achieving the desired objective.
3. For learning to occur, feedback should be accurate, immediate, consistent, and unbiased. With traditional therapy techniques the feedback is provided by the parent at home, and, given human nature, the feedback may not always be as consistent and as immediate as desirable.
The advantage of computerized home-based VT/orthoptics is that it overcomes each of the three potential problems listed above.

From a clinical trial standpoint, computerized therapy offers two additional advantages.

1. The use of home-based computer software allows for standardization of therapy procedures.
2. Since the computer software tracks the amount of time spent with the procedure and results achieved, a more accurate measure of adherence to the treatment is available than with traditional, non-computer-based activities.

We were unable to retrieve any research studies to support the effectiveness of non-computerized, home-based VT/orthoptics. Cooper and Feldman used computer-based vision therapy in an operant conditioning paradigm with 8 subjects to determine if vergence therapy improved vergence amplitudes. They used an A-B reversal design. The experimental group (A) received vergence therapy, while the control group (B) did not. (Eventually the control group became the experimental group, and the experimental group became the control group). During vergence therapy a correct response resulted in the computer automatically and immediately giving the subject a positive auditory reinforcement (beep) and an automatic increase in the vergence demand. Incorrect responses resulted in an audible “boop” from the computer and a concurrent decrease in the vergence demand. Thus, the behavior of the subject controlled the vergence demand. Success was met with a harder demand, failure, with an easier task. The control group received identical stimuli and reinforcement; however, neither correct nor incorrect responses resulted in a change in the vergence demand. The results of this study demonstrated that automated computerized therapy resulted in a rapid increase of fusional vergence with concurrent transference of this ability to other vergence tasks (vectogram vergence ranges). Since fusional vergence is a measure of the patient’s ability to effectively deal with the convergence insufficiency problem, this was a favorable outcome.

Daum et al supported Cooper and Feldman’s work by showing that vergence therapy using a computerized video display is an effective technique for increasing positive fusional vergence. Six subjects received positive vergence training using a slow vergence training rate (0.75 delta/s), and six subjects received positive vergence training using a fast vergence training rate (5.00 delta/s). Six subjects served as controls and did not receive therapy. The therapy was performed using a computerized video display. The duration of therapy was 80 min over a period of 4 weeks. All training activities were monitored. All vergence evaluations were double masked. The authors found that vergence therapy using a computerized video display is an effective technique for increasing positive fusional vergence.

Cooper and Selenow designed an experiment to determine if computer-based orthoptics/vision therapy was successful in treating convergence insufficiency and reducing symptoms. They again used an A-B-A cross-over design with 7 subjects to control for experimental bias, placebo effects, and order effects. After the experimental phase all patients exhibited significant increases in maximum vergence compared to that recorded at baseline or the control phase. The mean increase in vergence for all seven patients was 17.7Δ (std =6.9Δ). In contrast the vergence increase after the control phase was 2.4Δ (std =4.1Δ). Statistical analysis revealed that maximum vergence scores in baseline, control and experimental phases were significantly
different ($F=7.75; DF=2, 12; p<0.01$). It was found that therapy improved convergence amplitudes, and reduced symptoms as measured on a scaled questionnaire.

A review of the research of computerized VT/orthoptics indicates that it is an effective treatment for decreasing symptoms and improving positive fusional vergence in patients with convergence insufficiency (positive fusional vergence is one of the two secondary objective outcome measures in the CITT). While these studies used the identical software being used in the CITT, the therapy was actually administered in an office setting in these studies.

### 1.2.4.5 Office-based Vision Therapy/Orthoptics for CI

Office-based Vision Therapy/Orthoptics requires a subject to undergo a specific therapy regimen with regular office visits once or twice per week. Typically, vision therapists (O.D., M.D., orthoptists, or specially trained technicians) administer the therapy in the office. Office-based vision therapy/orthoptics is generally supplemented with various home therapy procedures as well. Approximately 10-20 office visits are necessary for most subjects. ²⁸, ²⁹, ³⁷

Table 1-4 lists studies from 1940-2002 that have reported on the effectiveness of vision therapy/orthoptics for the treatment of CI. ³⁸-⁴¹ The total number of subjects in these studies is 1882 with a total reported “cure” rate of 73.4% (range 62%-96%). The combined “improved and cure” rate is 92.4%, although various definitions of cure were used. Vision therapy/orthoptics has been shown to be effective for children, young adults, and presbyopes. ³⁶, ⁴¹, ⁴² Studies in Table 1-4, however, suffer from a variety of design flaws. These include: inadequate numbers of subjects, lack of a definition of CI, lack of operational definitions for success, retrospective design, lack of a placebo control, and unmasked examiners and subjects. Because of these problems, the effectiveness of VT/Orthoptics for CI has been challenged.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Subjects</th>
<th>% Cured</th>
<th>% Improved</th>
<th>% Failed</th>
<th>Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann</td>
<td>1940</td>
<td>142</td>
<td>68</td>
<td>30</td>
<td>3</td>
<td>b, d, e</td>
</tr>
<tr>
<td>Cushman and Burri</td>
<td>1941</td>
<td>66</td>
<td>66</td>
<td>30</td>
<td>4</td>
<td>b, c, e</td>
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<tr>
<td>Hirsch</td>
<td>1943</td>
<td>48</td>
<td>77</td>
<td>12</td>
<td>10</td>
<td>b, c, e</td>
</tr>
<tr>
<td>Duthie</td>
<td>1944</td>
<td>123</td>
<td>88</td>
<td>6</td>
<td>6</td>
<td>b, c, d, e</td>
</tr>
<tr>
<td>Mayou</td>
<td>1945</td>
<td>580</td>
<td>165</td>
<td>12</td>
<td>7</td>
<td>b, c, d, e</td>
</tr>
<tr>
<td>Mayou</td>
<td>1946</td>
<td>87</td>
<td>92</td>
<td>6</td>
<td>2</td>
<td>b, c, d, e</td>
</tr>
<tr>
<td>Mellick</td>
<td>1950</td>
<td>88</td>
<td>77</td>
<td>10</td>
<td>12</td>
<td>b, c, d, e</td>
</tr>
<tr>
<td>Passmore and Maclean</td>
<td>1957</td>
<td>100</td>
<td>82</td>
<td>18</td>
<td>0</td>
<td>c, d, e</td>
</tr>
<tr>
<td>Norn</td>
<td>1966</td>
<td>65</td>
<td>9</td>
<td>60</td>
<td>30</td>
<td>b, c, d, e</td>
</tr>
<tr>
<td>Hoffman et al</td>
<td>1973</td>
<td>17</td>
<td>88</td>
<td>-</td>
<td>12</td>
<td>a, d, e</td>
</tr>
<tr>
<td>Wick</td>
<td>1977</td>
<td>161</td>
<td>92</td>
<td>-</td>
<td>8</td>
<td>e</td>
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<tr>
<td>Pantano</td>
<td>1982</td>
<td>207</td>
<td>53</td>
<td>43</td>
<td>4</td>
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<tr>
<td>Daum</td>
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<td>110</td>
<td>41</td>
<td>56</td>
<td>3</td>
<td>d, e</td>
</tr>
<tr>
<td>Cohen and Soden</td>
<td>1984</td>
<td>28</td>
<td>96</td>
<td>4</td>
<td>0</td>
<td>a, d, e</td>
</tr>
<tr>
<td>Birnbaum et al</td>
<td>1999</td>
<td>60</td>
<td>62</td>
<td></td>
<td>38</td>
<td>e</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>1882</td>
<td>73.4%</td>
<td>19%</td>
<td>7.6%</td>
<td></td>
</tr>
</tbody>
</table>

a. inadequate numbers of subjects, b. lack of a definition of CI, c. lack of operational definitions for success, d. retrospective design, e. unmasked examiners and subjects
1.3 Public Health Significance
CI is a common problem that frequently results in significant symptoms with near work. However, the best treatment for CI is not known. Therefore, a randomized trial to determine the best treatment is justified. The cost of standard, home-based pencil push-up therapy with or without computer VT/orthoptics is significantly less than office-based vision therapy/orthoptics. Thus, the greatest public health cost impact will be derived if either home-based pencil push-up therapy group is demonstrated to be as or more effective than office-based vision therapy/orthoptics. Office-based vision therapy/orthoptics involves an average of 10 to 20 office visits, while little or no in-office follow-up is typically involved in pencil push-up therapy. The typical fee for an in-office vision therapy/orthoptics session in the United States is $75 per session. This translates to an additional cost of $1125 to $1500 per subject for in-office vision therapy/orthoptics. If pencil push-up therapy with or without computer VT/orthoptics is proven to be as effective as or more effective than office-based vision therapy/orthoptics in the treatment of CI, there will be a substantial savings in health care expenditures. If, however, the results demonstrate that office-based vision therapy/orthoptics is more effective than pencil push-up therapy for CI, professionals will have proven treatment algorithms with which to effectively treat this condition.

Subjects with CI and their doctors will benefit directly from the fact that this is a carefully designed systematic study with formal protocols, definitions, and procedures. The diagnosis and treatment guidelines developed in this study will provide consistency in a field replete with variability in definitions, diagnoses, and treatment practices. It will enable eye care practitioners to make more informed decisions concerning the nature of each subject’s visual dysfunction and the management procedures that would potentially be most appropriate.

1.4 Sample Size
All sample size calculations were performed using PASS 2000 software assuming a two-sided test with $\beta=0.10$ (i.e. 90% power). In the sample size calculations for a given outcome measure, the common standard deviation obtained from the CITT pilot study was used as an estimate of the variability. A clinically relevant difference between any two groups after 12 weeks of treatment with respect to the CI symptom score was defined as a difference in mean scores of at least 10 points. The CI symptom survey includes 15 items; this translates into scoring one response level lower on at least one-third of the survey items. This value is slightly larger than one-half the width of the 95% limits of agreement interval calculated using the CITT pilot study data. For each of the objective outcome measures, clinically relevant differences were determined by the CITT executive committee with input from other CITT study members. Information on the repeatability of each of the clinical measures was also used in the determination of clinically relevant differences.

Table 1-5 displays the results of the calculations to determine the number of patients per group required to detect clinically relevant differences as shown in the mean values obtained after 12 weeks between any two treatment groups. To control for multiple testing (6 pairwise comparisons), the alpha level used for determining sample size was set at $0.05/6 = 0.0083$. The final sample size per group was determined by finding the maximum required sample size among all outcome variables for detecting these pair-wise differences. Thus, 47 patients per group will...
be needed to find differences in the estimated means as or more extreme than those hypothesized.

### Table 1-5 – Sample Size Required to Detect Difference Between any Two Treatment Groups at Week 12 with 90% Power and \( \text{Alpha}=0.0083 \)

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Clinically relevant difference</th>
<th>Standard Deviation</th>
<th>Number per group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI Symptom score</td>
<td>10.0 units</td>
<td>12.0</td>
<td>47</td>
</tr>
<tr>
<td>Near point of convergence – break</td>
<td>4.0 cm</td>
<td>4.5</td>
<td>41</td>
</tr>
<tr>
<td>Positive fusional vergence – break</td>
<td>10.0 Δ</td>
<td>11.3</td>
<td>42</td>
</tr>
</tbody>
</table>

Sample size estimates were then adjusted for potential losses to follow-up. We estimate that 10% of subjects will be lost to follow-up before the end of the study (i.e. a retention rate of 90%); a total of 47*1.1 = 52 patients will be randomly assigned to each treatment arm. By adjusting the sample sizes, we ensure the ability to detect meaningful differences between the groups in analyses that include only those subjects with week 12 data (i.e., if we choose not to use earlier masked examination data as a proxy measure for week 12).

A total of 208 CI patients will be required to ensure adequate power to detect differences if they truly exist among treatment groups after 12 weeks of active treatment. Given our conservative recruitment estimate of 3 patients every two months from each of 9 clinical sites, we should then be able to reach our goal in no more than eighteen months.
1.5 Study Organization

As shown in Figure 1-1, the CITT represents a collaborative effort with the following components:

1. Study Chair, Mitchell Scheiman, OD FAAO, Pennsylvania College of Optometry
   Karen Pollack, Study Coordinator
2. Data Coordinating Center, G. Lynn Mitchell, MAS, FAAO, The Ohio State University
   College of Optometry
   Tracy Kitts, Program Coordinator
3. 9 Clinic Sites:
   (01) Pennsylvania College of Optometry
       Michael Gallaway, OD, FAAO, Principal Investigator
       Ryan Langan, Site Coordinator
   (02) The Ohio State University College of Optometry
       Marjean Taylor Kulp, OD, MS, FAAO, Principal Investigator
       Nancy Stevens, MS, RD, LD, Site Coordinator
   (03) Southern California College of Optometry
       Susan Cotter, OD, FAAO, Principal Investigator
       Rebecca Bridgeford, Site Coordinator
   (04) State University of New York College of Optometry
       Jeffrey Cooper, OD, MS, FAAO, Principal Investigator
       Kaity Colon, Site Coordinator
   (05) Ratner Children’s Eye Center
       David Granet, MD, Principal Investigator
       Cintia Gomi, Site Coordinator
   (06) Mayo Clinic
       Brian Mohney, MD, Principal Investigator
       (Unfilled Site Coordinator position @ print time)
   (07) Bascom Palmer Eye Institute
       Susanna Tamkins, OD, FAAO, Principal Investigator
       Eva Olivares, Site Coordinator
   (08) University of Alabama at Birmingham School of Optometry
       Kristine Hopkins, OD, FAAO, Principal Investigator
       Adrienne Broadfoot, MS, OTR/L, Site Coordinator
   (09) NOVA Southeastern University
       Stacey Coulter, OD, FAAO, Principal Investigator
       Annette Bade, Site Coordinator
4. The National Eye Institute, Päivi Miskala, PhD
5. Executive Committee
6. Data and Safety Monitoring Committee, Marie Diener-West, PhD, Chair

An outline of the functions and composition of the study centers and committees follows
Figure 1.1 Study Organization

**National Eye Institute**
Maryann Redford, DDS MPH

**Data and Safety Monitoring Committee**
Marie Diener-West, Ph.D., Chair
Rev. Andrew Costello, C.Ss.R.
William V. Good, M.D.
Ronald D. Hays, Ph.D.
Argye Hillis, Ph.D.*
Ruth Manny, O.D., Ph.D.

**Executive Committee**
Mitchell Scheiman, O.D., Study Chair
Susan Cotter, O.D., Vice-Chair
Richard Hertle, M.D., Vice-Chair
Marjean Taylor-Kulp, O.D., PI OSU
Michael W. Rouse, O.D., MS, Consultant
G. Lynn Mitchell, MAS, PI DCC
Maryann Redford, DDS MPH

**Study Chair**
Mitchell Scheiman, O.D., Study Chair
Susan Cotter, O.D., Vice-Chair
Richard W. Hertle, M.D., Vice-Chair
Michael W. Rouse, O.D., MS Consultant
Karen Pollack, Study Coordinator

**Data Coordinating Center (DCC)**
G. Lynn Mitchell, MAS, PI
Lisa A. Jones, Ph.D., Co-PI
Tracy Kitto, Project Coordinator
Loraine Sinnott, MAS, Biostatistician
Melanie Schray, Lead Programmer
Linda Barrett, Data Entry
Gerald J. Beck, Ph.D., Consultant
Karla Zadnik, O.D., Ph.D., Consultant
Melvin Moechberger, Ph.D., Consultant

**Full Investigators Group**

PCO
Michael Gallaway, O.D.

OSU
Marjean Kulp, O.D., MS

SCCO
Susan Cotter, O.D.

SUNY
Jeffrey Cooper, O.D., MS

Ratner Eye Center
David B. Granet, M.D.

NOVA
Stacey Coulter, O.D.

UAB
Kristine Hopkins, O.D.

Bascom Palmer
Susanna Tamkins, O.D.

Mayo Clinic
Brian Mohoney, M.D.

*Argye Hillis, PhD, resigned her post as a DSMC member March 2006.*
1.6 Participating Centers

1.6.1 Study Chair’s Office

*Location:* The Pennsylvania College of Optometry, Philadelphia, PA

The Study Chair will:
1. Provide leadership for the study
2. Oversee the implementation of protocols as outlined in the Manual of Procedures
3. Chair the CITT Executive and Full Investigator Group Committees
4. Lead publicity and recruitment efforts
5. Serve as the study spokesperson
6. Serve as a communication center for CITT Principal Investigators and other study personnel
7. Develop manuscripts for publications, in conjunction with the CITT Executive Committee
8. Coordinate and document study meetings and conference calls involving CITT investigators

1.6.2 Data Coordinating Center

*Location:* The Ohio State University Optometry Coordinating Center, Columbus, OH

The Coordinating Center will:
1. Provide epidemiologic and biostatistical expertise to the organization, design, conduct, and analysis of the trial
2. Be responsible for quality assurance procedures
3. Develop and refine the study Manual of Procedures
4. Develop and distribute study forms, documents, and protocols
5. Provide independent and objective confirmation of subject eligibility
6. Develop and monitor the randomization process
7. Develop and implement procedures for data management and data analysis
8. Prepare periodic monitoring reports for the trial’s Executive Committee, Data and Safety Monitoring Committee, and the National Eye Institute
9. Archive all study documents
10. Serve on the Executive Committee
11. Participate in site visits
12. Participate in the design, analysis, and publication of the study results

1.6.3 Clinic Sites

*Locations:* (See page 1-12)

The Clinic Sites are responsible for:
1. Collaborating in the development of relevant sections of the Manual of Procedures
2. Collaborating in the development of study forms and procedure
3. Developing informed consent procedures
4. Obtaining local IRB approval
5. All aspects of subject recruitment
6. Data collection for all study visits
7. Training and supervision of staff involved with data collection

1.6.4 National Eye Institute

The National Eye Institute is accountable for the use of Institute funds and participates to ensure the success of the study. The NEI Grants Management Specialist is responsible for all business management matters associated with administration of the CITT. The NEI Program Director, Päivi Miskala, PhD, participates in all scientific activities of the study and provides assistance in study administration. All questions or correspondence dealing with research progress, changes in research direction, unique scientific opportunities, or any other scientific needs should be addressed to Dr. Miskala.

1.7 Study Committees

CITT committees include the Executive Committee and the Data and Safety Monitoring Committee. The composition and functions of each committee are described below.

1.7.1 Executive Committee (EC)

The CITT EC, which oversees and directs all aspects of the study, includes:
- Mitchell Scheiman, OD, CITT Study Chair, Pennsylvania College of Optometry
- G. Lynn Mitchell, MAS, DCC Principal Investigator, The Ohio State University College of Optometry
- Susan Cotter, OD, Vice-Chair, Southern California College of Optometry
- Richard Hertle, MD, Vice-Chair, Children’s Hospital of Pittsburgh
- Marjean Taylor-Kulp, OD, PI, The Ohio State University College of Optometry
- Michael Rouse, OD, Study Consultant, Southern California College of Optometry
- Maryann Redford, DDS MPH, NEI Program Director

Executive Committee functions are to:
1. Provide overall direction and coordination for the trial
2. Supervision of training and certification
3. Review study progress
4. Formulate policies and decisions for the trial
5. Review and approve the procedures for the conduct of the trial
6. Resolve technical issues
7. Interact with the DSMC regarding the conduct of the trial and react to its advice regarding the design, operation, or termination of the trial
8. Coordinate the preparation of progress reports and updates to the MOP
All members of the Executive Committee serve for the duration of the trial, provided they continue in their designated capacities. The Executive Committee will communicate throughout the trial with regularly scheduled conference calls.

### 1.7.2 Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee consists of members of the scientific community entrusted to ensure the safety of all CITT participants and the validity and integrity of the CITT data.

The committee includes:
- Marie Diener-West, PhD., Chairman, Professor of Biostatistics, Johns Hopkins University
- Rev. Andrew Costello, C.Ss.R., St. Mary’s Church, Annapolis, MD
- William V. Good, M.D., Smith Kettlewell Eye Research Institute
- Ronald D. Hays, PhD., UCLA Department of Medicine
- Argye Hillis, PhD., Waco, TX (retired; effective March 2006)
- Ruth Manny, O.D. PhD., University of Houston College of Optometry

The specific functions of the DSMC include:
1. Provision of advice to the Executive Committee on operational procedures that would improve the quality of the trial
2. Review and approval of the protocol
3. Review of the data collected throughout the trial for evidence of adverse, beneficial or no treatment effects
4. Provision of advice to the investigators of the study and the NEI on the design, organization, and conduct of the trial
5. Provision of guidance to NEI as to the continuation or termination of the trial
6. Monitoring the conduct of the CITT
7. Reviewing the design of the CITT, including methods of subject recruitment, the informed consent process, and data collection procedures
8. Evaluating the accumulating data at regular intervals
9. Determining when the data are sufficiently convincing to answer questions of interest
10. Monitoring the study data for early dramatic effects or potential harmful effects
11. Determining when data collected should be released to the Study investigators, to Study subjects, and to the ophthalmic community
12. Evaluating recruitment and monitoring the overall performance of the CITT Participating Clinics
13. Recommending to the NEI and the Executive Committee changes in the Study protocol based on periodic data analysis
14. Evaluating data and protocols for the protection of the participating subjects
15. Reviewing the results of the CITT and how they will be presented in publication.
16. Protecting the operational and scientific integrity of the Study including the evaluation of ancillary studies
1.8 References

Chapter 1 Appendix
Convergence Insufficiency - Symptom Questionnaire V-15

Name _____________________________________  DATE __/__/__

Subject instructions: Please answer the following questions about how your eyes feel when reading or doing close work. Choose your response from the card that I have just handed you.

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Infrequently</th>
<th>Sometimes</th>
<th>Fairly often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do your eyes feel tired when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do your eyes feel uncomfortable when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you have headaches when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you feel sleepy when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Do you lose concentration when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do you have trouble remembering what you have read?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you have double vision when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Do you see the words move, jump, swim or appear to float on the page when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Do you feel like you read slowly?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Do your eyes ever hurt when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Do your eyes ever feel sore when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Do you feel a &quot;pulling&quot; feeling around your eyes when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Do you notice the words blurring or coming in and out of focus when reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Do you lose your place while reading or doing close work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Do you have to re-read the same line of words when reading?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL Xs in each column</td>
<td>x 0</td>
<td>x 1</td>
<td>x 2</td>
<td>x 3</td>
<td>x 4</td>
</tr>
</tbody>
</table>

Score _______________