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Chapter 2: Study Design and Methods

2.1 Study Design and Methods

The Convergence Insufficiency Treatment Trial (CITT) is a multi-center, placebo-controlled, single-masked, clinical trial designed to compare the benefits of Pencil Push-up therapy and Vision Therapy/Orthoptics.

Two-hundred and eight subjects aged 9 to <18 years with convergence insufficiency will be enrolled over an 18-month period. Potentially eligible subjects who provide informed consent for testing will be given an exam to determine eligibility. Subjects who are eligible will be informed about the CITT and those who provide a second informed consent will be sequentially admitted to the study. A study timeline appears on page 2-4.

Subjects will be randomized into one of four treatment groups. The four treatment groups are: 1) Home-based Pencil Push-up Therapy, 2) Home-based Pencil Push-ups with Computer Vision Therapy/Orthoptics, 3) Office-based Vision Therapy/Orthoptics, and 4) Office-based Placebo Vision Therapy/Orthoptics.

Subjects in each treatment group will receive 12 weeks of treatment. Subjects randomized to the Home-based Pencil Push-up Therapy group and the Home-based Pencil Push-ups with Computer VT/Orthoptics group will receive 12 weeks of home-based treatment and weekly phone appointments with the therapist. Subjects randomized into Office-based VT/Orthoptics and the Office-based Placebo VT/Orthoptics therapy groups will receive weekly, 60 minute, in-office treatment sessions supplemented with home therapy procedures for 12 weeks. During this active treatment phase, a Masked Examiner will evaluate subjects after 4 and 8 weeks of treatment have been completed. The masked, primary outcome examination will occur after 12 weeks of treatment have been completed. For subjects who do not complete the 12 treatment sessions, the final outcome measure will still occur after the 12th scheduled week of treatment would have been completed and these data will be analyzed as the primary outcome data.

Additional masked examinations will occur 6 months and 12 months after completion of active treatment in order to assess the long-term effects of treatment. A subject from any treatment group who scores ≥ 16 on the CI Symptom Survey at the primary masked examination (week 12) will be referred to a non-CITT clinician for alternative treatment, which will be provided at no cost to the subject. At the 6- or 12-month follow-up visits, any previously asymptomatic subject who scores ≥ 16 on the CI Symptom Survey will be referred to a non-CITT clinician for alternative treatment. Sites may choose to offer this treatment at no cost or require payment from the subject's family.

2.1.1 CITT Study Timetable

CITT Study Timeline As of 3-1-05	Year 1 Oct./2004 thru Sept./2005												Year 2 Oct./2005 thru Sept./2006												Year 3 Oct./2006 thru Sept./2007												Year 4 Oct./2007 thru Sept./2008											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Form DSMC, finalize protocols	█																																															
Hiring, training, certification of CITT personnel	█																																															
Recruitment and Enrollment													█																																			
Active Treatment Phase													█												█																							
Masked examinations at 4, 8 and 12 weeks													█												█																							
6-month follow-up examinations																									█																							
12-month follow-up examinations																																					█											
Data collection and entry																																					█											
Data analysis																																					█											
Training and annual FIG meetings																																					█											
Abstract/ manuscript preparation																																					█											

2.1.2 Choice of Treatment Arms

Despite the high prevalence of CI and the symptoms it frequently causes with near work, the best treatment for CI is not known. Other than our recently completed CITT pilot study, two smaller randomized trials of vision therapy, and two recent prospective studies of base-in prism, there have been no prospective studies of treatment methods for CI.

Treatments for CI can be categorized as active or passive treatment. Active treatment includes pencil push-ups, more extensive home-based convergence treatment, and VT/Orthoptics. Passive treatment includes base-in prism, reading glasses, and in some cases, extraocular muscle surgery. While the CITT study group would like to evaluate the effectiveness of all treatments for CI, we know that it is not feasible to do so in a single clinical trial. We have not included a base-in prism reading glasses treatment arm because a recent randomized clinical trial found this treatment to be no more effective than placebo reading glasses. Because the consensus is that some form of active convergence treatment is the treatment of choice for CI, we determined that a comparison of the effectiveness of home-based pencil push-up therapy, more extensive home-based VT/orthoptics and office-based VT/orthoptics were the most compelling questions for the eye care community in this first proposal. Nevertheless, our long-term plan is to sequentially, and systematically investigate both active and passive treatment options. In fact, our CITT study group completed a pilot study on the effectiveness of prism glasses in children.

We used the results of the surveys described in Chapter 1.2.4.2 to help us select Home-based Pencil Push-up therapy, Home-based Pencil Push-ups with Computer VT/Orthoptics and Office-based VT/Orthoptics as the focus of our proposed study. Office-based VT/Orthoptics was chosen because it is the most widely studied treatment, although the vast majority of studies have been retrospective and uncontrolled. Furthermore, there is considerable controversy in the eye care community regarding Office-based VT/Orthoptics with almost 70% of optometrists but only 4% of ophthalmologists reporting it to be as or more effective than any other treatment for CI. We selected Home-based Pencil Push-up therapy because it is the most commonly prescribed treatment by both ophthalmologists and optometrists in the USA. As such, this home-based therapy is the “standard of care” in the ophthalmic community notwithstanding that only one small, uncontrolled study evaluated its effectiveness in the treatment of CI. We selected Home-based Pencil Push-ups with Computer VT/Orthoptics because our survey indicated that it was the second most commonly prescribed treatment for CI. The inclusion of this treatment group will also allow us to study the effectiveness of a treatment that falls between the two extremes of simple pencil push-ups and intense office-based VT/orthoptics.

In order to affect clinical care, it is necessary for the study treatment arms to approximate clinical practice. However, the fundamental differences between home-based and office-based treatments could lead to potential bias in the study if either or both home-based treatments had decreased retention. As a result, treatment logs and weekly phone calls were added to maximize compliance and retention in both Home-based Pencil Push-up Therapy groups, while still approximating clinical practice.

Finally, some practitioners believe that office-based VT/orthoptics may not have any significant beneficial effect and that any improvement in symptoms reported by subjects after office-based

VT/orthoptics may be attributable to the placebo effect. We, therefore, included an Office-based Placebo VT/Orthoptics treatment arm to answer one of the most commonly asked questions about vision therapy/orthoptics.

Do subjects undergoing Office-based VT/Orthoptics for CI report improvement after treatment simply because of the time and effort devoted to the treatment?

Because the amount of treatment needed is also not known, we included masked examinations after every 4 weeks of treatment to evaluate the kinetics of treatment.

2.1.3 Placebo Therapy

There were two primary challenges that we faced during the CITT Planning Grant phase and CITT Pilot Study.

1. To develop a placebo treatment program that could simulate office-based intervention as closely as possible so that subjects could not determine to which group they have been randomized.
2. To control the effect of the “therapist as a placebo.” Healing from a subject’s perception may be related to his or her interaction with the physician or therapist. The enthusiasm, caring and compassion of the therapist may play a key role in the outcome. Our goal was not to eliminate this factor but to ensure that the therapist behaved identically for subjects in both the Office-based VT/Orthoptics and Office-based Placebo VT/Orthoptics groups. This will be an essential objective of our training, certification and quality assurance protocol in the CITT.

The development of a viable placebo treatment regimen was one of the main objectives of our completed CITT Planning Grant. The results of that study indicate that we have developed an effective placebo treatment.

2.2 Treatment Methods

2.2.1. Home-based Pencil Push-up Therapy

The treatment protocol for Home-based Pencil Push-up therapy is described in detail in Chapter 7. The Home-based Pencil Push-up therapy group will be asked to practice a well-defined pencil push-up procedure at home. They will be instructed to do Pencil Push-ups 15 minutes per day, five days per week for 12 weeks. Subjects will maintain a home therapy log form and record the number of sets of pencil push-ups each day and how close to their nose they were able to converge and maintain fusion. Based on the results of the CITT Planning Project, the one published study of Pencil Push-up therapy,³³ and comments from reviewers, we have enhanced the Home-based Pencil Push-up technique by adding weekly phone appointments during which the home therapy log will be reviewed and the therapist will motivate the subject in order to maximize adherence. Although this protocol is more rigorous than that used in current clinical practice, we believe that this will allow us to maximize retention and adherence to the Home-based Pencil Push-up therapy protocol while still approximating clinical practice.

2.2.2 Home-based Pencil Push-ups with Computer VT/Orthoptics Therapy

The treatment protocol for Home-based Pencil Push-ups with Computer VT/Orthoptics is described in detail in Chapter 7. The Home-Based Pencil Push-ups with Computer VT/Orthoptics group will be asked to practice the same well-defined pencil push-up procedure as the Home-Based Pencil Push-up group. In addition, they will work with the Home Therapy System (HTS) computer software at home. Subjects assigned to this treatment arm that do not have a computer at home will be provided a desktop computer for use during the study. Subjects will maintain a home therapy log form and record the number of sets of pencil push-ups each day and how close to their nose they were able to converge and maintain fusion. They will, in addition, need to record the level completed for each section of computer therapy. Subjects will be required to demonstrate their ability to perform these procedures to the therapist in the office before beginning therapy at home. Therapy should require a total of about 20 minutes per day (15 minutes for HTS and 5 minutes for pencil push-ups), five days per week. Phone appointments will also occur weekly for this therapy group. The home therapy log will be reviewed and the therapist will motivate the subject in order to maximize adherence.

2.2.3 Office-based Vision Therapy/Orthoptics (VT/Orthoptics)

The treatment protocol for Office-based VT/Orthoptics is described in detail in Chapter 8. Office-based VT/Orthoptics is administered by a trained therapist (weekly, 60-minute office visits), combined with procedures to perform at home, (15 minutes, five times per week). This treatment sequence is a well-accepted approach for office-based VT/orthoptics for CI. To enhance compliance we will ask participants to log their home therapy activities including minutes spent on the therapy and objectives achieved. Subjects will be required to demonstrate their ability to perform these procedures to the therapist in the office before beginning therapy at home. At each office treatment session the therapists will review these logs and encourage adherence.

Subjects, who complete the entire Office-based VT/Orthoptics therapy sequence in less than 12 weeks, will be ask to continue to come in for weekly visits and the therapy procedures will be the final procedures (most difficult) in each category (gross convergence, vergence, and accommodation).

2.2.4 Office-based Placebo VT/Orthoptics

The treatment protocol for Office-based Placebo VT/Orthoptics is described in detail in Chapter 9. Like the Office-based VT/Orthoptics subjects, the Office-based Placebo VT/Orthoptics group will also receive therapy administered by a trained therapist during a 60-minute office visit, combined with procedures to perform at home, 15 minutes, five times per week. Subjects will be asked to log the home therapy activities that are completed in order to enhance compliance. At each office treatment session the therapists will review these logs and encourage adherence.

2.3 Masking

Patient's self-assessment and clinicians' judgments can lack objectivity when either person has expectations about the treatment under study. Such expectations can be introduced when either the subject or the clinician is not blinded (unmasked) to treatment assignment. This lack of objectivity introduces assessment bias into the measurements obtained from either the patient (if not masked) or the clinician (if not masked). Such assessment bias most often differentially affects treatment estimates because the patient and/or clinician have different expectations about different treatments. It is not feasible to mask the patient to his or her assignment to either Pencil Push-up therapy, Pencil Push-ups with Computer VT/Orthoptics or VT/Orthoptics because the treatment regimens are vastly different. We have, however, been able to design a placebo arm that simulates actual VT/Orthoptics. We were also, during the CITT pilot study, able to mask the clinicians responsible for obtaining outcome measures at each of the examinations. It is not feasible, however, to mask the CITT personnel responsible for training the subject in the assigned treatment option. It is especially important then that masking of the clinicians is maintained. If an examiner was aware of the patient's assigned treatment it could introduce assessment bias into the study results. Chapter 10 contains information regarding methods used to ensure subject and examiner masking.

2.4 Primary Outcome Measure

From the CI patient's standpoint, symptoms are the primary problem. The main reason patients seek treatment is because they are symptomatic. Therefore, the primary outcome measure will be the score on the CI Symptom Survey.

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 patients. Existing visual-specific quality of life measures have focused on visual acuity and postoperative effects of surgery. Therefore, such measures are not appropriate for evaluating patients with CI who have normal visual acuity and are expected to have difficulties with performing sustained visual activities within arm's length.

As reported in Chapter 1, the CI Symptom Survey has been shown to be both a reliable and valid method of assessing symptoms in subjects with CI. The use of this instrument is necessary to create the scientific rigor and consistency that is currently lacking in the area of binocular vision research.

2.5 Secondary Outcome Measures

2.5.1 Near Point Convergence

The near point of convergence will be measured with the Astron International (ACR/21) Accommodative Rule. Members of the CITT study group performed a small study (20 5th and 6th graders) to assess the intra- and inter-reliability of our NPC break measure. Repeatability was reported using both the intraclass correlation coefficient (ICC) and the coefficient of repeatability (COR=1.96*standard deviation of the difference between repeated observations). All subjects were

evaluated by two separate examiners (within examiner repeatability) at two different testing sessions (between session repeatability). The within examiner ICC values were all greater than 0.93 indicating excellent repeatability. There was also excellent agreement between the two examiners at each session. Using session 1 data, the between-examiner ICC was 0.86 with a COR of 4.43cm. Both the ICC and COR improved when between-examiner reliability was assessed using session 2 data (ICC=0.97, COR=2.55 cm). Similarly, there was excellent repeatability when comparing one examiner at two sessions. For examiner 1, the ICC was 0.92 and the COR was 5.33 cm while Examiner 2 had an ICC of 0.89 and COR of 5.00 cm. Specific methods for performing the procedure can be found in Chapter 4.1.2.

2.5.2 Positive Fusional Vergence

Positive fusional vergence (PFV) will be measured with a horizontal prism bar (Gulden B-16 horizontal prism bar level from 1Δ to 45Δ) while the patient fixates a hand-held fixation target (Gulden fixation Stick # 15302) with a single column of letter of 20/30 equivalent. Instructions for this measurement can be located in Chapter 4.1.3.

The reliability of positive fusional vergence was evaluated in both children and adults. Two examiners tested 20 fifth and sixth graders in a school setting who passed a screening of visual acuity, refraction, and binocularity. Two other examiners tested 30 young adults between the ages of 22 and 30 years. The tests, conducted using a standard fusional vergence, (blur, break, recovery) using Risley prisms. Both the intra- and inter-examiner agreement were not optimal. (Intraclass correlation coefficient of 0.64 for intra-examiner reliability and intraclass correlation coefficient of 0.59 for inter-examiner reliability).

To address the poorer reliability of the von Graefe prism method for assessing PFV, the Prism Bar method for assessing PFV was also examined. Two examiners tested 30 adults between the ages of 20 and 30 years, and two other examiners tested 44 children between the ages of 9 and 13 years. The Prism bar method shows higher intraclass correlation coefficient for both the intra-examiner reliability (0.73) and inter-examiner reliability (0.85).

The poorer reliability of the PFV measurement may lead to problems with classifying subjects with CI. During initial testing, a subject may have a high level of symptoms and a poor NPC but do well on the PFV assessment due only to measurement error. This scenario would result in excluding some eligible subjects from the study. More importantly, the measurements NPC and symptoms have very good reliability and low measurement error. Thus, a non-CI subject scoring poorly on all three tests because of measurement error is unlikely to occur.

PFV variability can also impact the ability to track changes resulting from the two therapies for CI. However, previous studies indicate that PFV can change substantially ($>10\Delta$) with orthoptic therapy. Thus, changes in PFV from treatment are expected to be outside of measurement error and thus indicate a true change in function following treatment.

2.6 Overview of Procedures after Randomization

2.6.1 Randomized to Home-based Pencil Push-up Therapy

At the initial training visit, the Vision Therapist will instruct the subject on the proper technique for pencil push-up therapy and the correct way to complete the home therapy log. The subject will be required to demonstrate at least one set of pencil push-ups and record the results on the form so that the therapist can be sure the technique is performed correctly. To further maximize adherence, a weekly phone appointment with the therapist will be scheduled for all subjects in this treatment arm. During this phone appointment, the therapist will review the treatment, the home therapy log form, answer questions, discuss problems, motivate the subject to follow the treatment protocol and review the next scheduled date for phone contact. Upon completion of the call, the vision therapist or site coordinator should transmit the phone contact form to the Data Coordinating Center. Attempts to contact the subject should be made on the agreed upon date (generated by the CITT scheduling module). This date is indicated in the target date box of the Pencil Push-up Therapy Phone Contact form. If contact cannot be made on the agreed date, the vision therapist should make 3 daily calls, spaced throughout the day/evening (after school hours when school is in session), to optimize the possibility of reaching the subject during the treatment window. Attempts to complete this contact will be made up to 3 days prior to the subject's next scheduled phone appointment. If the vision therapist is unable to reach the subject within window then that phone contact is considered a missed appointment and the Pencil Push-up Therapy Phone Contact form should be completed and faxed to the Data Coordinating Center.

Masked examinations will be scheduled after completion of every 4 weeks of treatment (at 4-, 8- and 12-weeks after the initial training session). After the 4- and 8-week masked examination is performed, the therapist will once again meet with the subject to demonstrate the pencil push-up therapy technique, review/collect the home therapy log, assess/emphasize compliance, and distribute a new home therapy log. The weekly calls and monthly visits with the therapist are designed to ensure the highest possible compliance in this group. At the completion of the 12-week masked examination, the vision therapist will assess the symptom level. Subjects with an average CI Symptom Survey <16 will be assigned to a maintenance therapy. All other subjects will be offered 12 weeks of alternative treatment at no cost (by a clinician not associated with the CITT). The alternative treatment must be started within one month of completion of the 12-week masked examination. Subjects will be scheduled for a masked examination 6 and 12 months after completion of this active phase of treatment. At these visits, a masked examiner will again assess outcome measures. If a previously asymptomatic subject scores 16 or higher on the CI Symptom Survey at either follow-up examination, he or she will be referred to a non-CITT clinician for alternative treatment. Sites may choose to offer this treatment at no cost or require payment from the subject's family.

2.6.2 Randomized to Home-Based Pencil Push-ups with Computer VT/Orthoptics

At the first treatment visit, the therapist will instruct the patient on the proper technique for pencil push-up therapy and the use of the computer VT/orthoptics software (HTS). The therapist will also review the correct way to complete the home therapy log. The patient will be required to demonstrate at least one set of pencil push-ups and record the results on the form so that the

therapist can be sure the technique is performed correctly. In addition, the patient will be required to open and initiate the HTS therapy program. To further maximize adherence, a weekly phone appointment with the therapist will be scheduled for all patients in this treatment arm. During this phone appointment, the therapist will review the treatment, the home therapy log form, answer questions, discuss problems, and motivate the patient to follow the treatment protocol. Masked examinations will be scheduled after completion of every 4 weeks of treatment. After each masked examination is performed, the therapist will once again meet with the patient to demonstrate the pencil push-up therapy technique, review/collect the home therapy log, review the data from the HTS data disk, assess/emphasize compliance, and distribute a new home therapy log. The weekly calls and monthly visits with the therapist are designed to ensure the highest possible compliance in this group.

A masked examiner will perform a masked examination after completion of the 12th week of treatment. All asymptomatic patients (CI Symptom Survey <16) will be assigned to a maintenance therapy and re-scheduled for a masked examination 6 and 12 months after completion of treatment. At these visits, a masked examiner will assess outcome measures. Patients deemed symptomatic at the 12-week visit (CI Symptom Survey ≥ 16) will be referred for 12 weeks of alternative treatment by a non-CITT eye care professional and followed at 6 and 12 months. The alternative treatment must be started within one month of completion of the 12-week masked examination. If a previously asymptomatic subject scores 16 or higher on the CI Symptom Survey at either the 6- or 12-month follow-up examination, he or she will be referred to a non-CITT clinician for alternative treatment. Sites may choose to offer this treatment at no cost or require payment from the subject's family.

2.6.2.1 Procedure for Subjects with No Computer at Home

In the event that a subject assigned to this treatment arm does not have a computer at home, the Site Coordinator or Vision Therapist/Orthoptists should have the parent/guardian complete and sign the Computer Policy Acceptance form (CPA). This form along with the subject's contact information form should then be faxed to Dr. Mitchell Scheiman, the Study Chair. Dr. Scheiman will arrange shipment of a computer to the subject's home from RC Instruments. The computer will arrive with the necessary programs pre-loaded. It is important to instruct the subject and his/her parent/guardian that the system is set up as to not allow any modifications or the addition of any new material. Furthermore, the system will not have internet capabilities. The initial training session for subjects in this group should be scheduled no more than 7 days after the subject has received the computer.

After completion of the study the computer will be shipped back via UPS. There will be no cost for shipping the computer back to RC Instruments and will be pre-arranged by the Study Chair. The Site Coordinator should remind families to save the shipping boxes and packing materials for the return shipment.

2.6.2.2 Computer Support

Each Vision Therapist/Orthoptist will be trained by Rod Bortel (HTS President) to be able to answer the most common support issues related to the use of HTS. When the Vision

Therapist/Orthoptist cannot solve a subject's problem, the Vision Therapist/Orthoptist will call Rod Bortel at 1-888-810-3937 and he will then call the subject to resolve the problem.

2.6.3 Randomized to Office-based VT/Orthoptics or Office-based Placebo VT/Orthoptics

At the initial training visit, the therapist will begin the protocol described in the appropriate CITT MOP Chapters (8 or 9), according to the subject's assigned treatment group. Subjects will be asked to demonstrate all home therapy techniques to the therapist before leaving. In addition, the subject will be given a home therapy log form and instructed on the proper technique for completing it. At each subsequent weekly visit, the therapist will perform the procedures as directed by the protocol and assign new home techniques as needed (per protocol).

Masked examinations will be scheduled after completion of every 4 weeks of treatment. After 12-weeks of treatment, all subjects with a CI Symptom Survey <16 will be assigned 6 months of maintenance therapy. Symptomatic subjects (CI Symptom Survey ≥ 16) will be referred to a doctor who is a non-CITT investigator for all follow-up care. Twelve weeks of additional CI treatment will be provided at no cost to the subject. The alternative treatment must be started within one month of completion of the 12-week masked examination. All subjects will be scheduled for a masked examination at 6 and 12 months after completion of the active phase of treatment. At these visits, a masked examiner will again assess outcome measures. If a previously asymptomatic subject scores 16 or higher on the CI Symptom Survey at either follow-up examination, he or she will be referred to a non-CITT clinician for alternative treatment. Sites may choose to offer this treatment at no cost or require payment from the subject's family.

2.7 Routine Ophthalmic Care and Emergencies

A subject requiring routine or emergency eye care unrelated to CITT can receive this care within the clinic site or from the family eye doctor, whichever is most convenient. These services will not be paid for by CITT.

2.8. Analysis of Data

2.8.1. Data Collection and Analysis

Question (primary aim of study): *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 aim of the study is to compare the symptom survey score obtained at the end of 12 weeks of treatment between the four groups. The greatest power to detect differences between the groups occurs when the degrees of freedom associated with the estimated mean square error (MSE) are maximized. In other words, by maximizing the degrees of freedom, we ensure the most appropriate estimate of variability. The maximum degrees of freedom for the MSE occur

when the symptom score data at weeks 4 and 8 are also used in the estimation. In order to compare the groups at 12 weeks while using all of the data to estimate variability, a 4 group by 3 time period repeated measures analysis of covariance (ANCOVA) will be used. This analysis uses all of the longitudinal data collected, is robust to missing data, and is flexible enough to allow valid inferences concerning a variety of questions. The symptom survey score obtained at the eligibility examination will be used as a covariate since our initial pilot data show a strong correlation between this value and all subsequent values.

The repeated measures analysis will include two factors (group assignment and time) and the interaction of these two factors (group by time). The interaction effect tests for differences in the pattern of response across time between the four groups. If we were to connect the mean responses at weeks 4, 8 and 12 for each of the groups, this interaction would test if the lines are parallel. Any overall differences in the mean response across group (averaged over time) are tested by the group factor while differences in the means across time (averaged over group) are tested using the time factor. The interaction effect will be pivotal in analyses of some of our additional questions. For our major analyses, the significance or non-significance of the interaction term will only be used to select the most appropriate estimate of error to use in our post-hoc comparisons. Since our major interest is not really in the overall differences between groups but specifically pair-wise comparisons, it will then be necessary to use post-hoc techniques to compare the means while controlling the overall error rate. The overall comparison of groups is merely a preliminary comparison used to determine if pair-wise comparisons are necessary. If the analysis indicates that there are no differences between the groups, then such post-hoc comparisons would be moot. If, on the other hand, the analysis indicates some group differences, Tukey's method of adjustment for multiple comparison will be used to hold the overall error rate at $\alpha=0.05$ while the six pair-wise hypothesis tests are performed. Demographic and clinical measures obtained at the eligibility examination will be included in the ANCOVA as covariates if initial comparison of the groups with respect to these variables uncovers clinically relevant differences. Such differences are unlikely since subjects are randomized to the treatment arms. Compliance to the assigned treatment regimen will be collected at each outcome visit. Such information, though not used to exclude subjects, will be examined as a potential covariate in the analyses. Potential interactions (effect modification) between treatment groups and each of the identified covariates will also be assessed.

With four treatment arms, there are six post-hoc pair-wise comparisons which will be made. The results of all of these comparisons will then need to be synthesized into a final conclusion about the relative effectiveness of Home-based Pencil Push-up therapy, Home-based Pencil Push-ups with Computer VT/Orthoptics and Office-based VT/Orthoptics. 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.

Similar analyses will be performed for near point of convergence break and positive fusional vergence break. Before beginning the analysis of either our primary outcome variable (symptom score) or any of the secondary measures, values will be imputed for those subjects who do not have data for the 12-week visit.

Question: Are improvements in outcome measures still present at the 6-month and 12-month follow-up for subjects who are asymptomatic?

Information obtained at the 6- and 12-month masked examination from subjects who scored less than 16 on the CI Symptom Survey at week 12 will be used to study the long-term effects of treatment. Data from the CITT pilot study indicate that the sample size in both Pencil Push-up groups and the Placebo VT/Orthoptics group may be small. If the sample size permits, regression modeling will be used to determine the demographic and clinical measures from the eligibility examination and/or the 12 week visit, which predict long term effectiveness. Such analysis will be performed separately within each treatment group. Regardless of the number of subjects, a 95% confidence interval will be constructed to describe the mean change in outcome from week 12 to both the 6- and 12 month follow-up for each treatment group. Because of the anticipated small numbers in some of the groups, we will not specifically compare the changes between treatment groups.

Question: Could shorter treatment durations provide similar effects? Are the treatment differences observed at the 12-week outcome examination also present at the 4- and 8- week masked examinations? Is there a significant improvement in the outcome measures between successive masked examinations for each of the four treatment groups?

The results from the repeated measures ANCOVA will be used to compare, separately for each group, the mean of each outcome variable across exams and to compare the groups at the two earlier masked exams. As with our initial comparisons, the significance or non-significance of the interaction term will be used to determine the appropriate estimate of error to use in our post-hoc comparisons. The overall error-rate associated with post-hoc testing will be controlled using Tukey's method of multiple comparisons. This analysis will be performed for the primary outcome variable, symptom score, and both of the secondary outcome measures.

Question: *What percent of subjects in each of the four groups would be classified as successful or improved after completion of 12 weeks of treatment?*

After completion of the 12 week masked examination, all subjects will be classified as successful, improved or non-responders. Successful is defined as:

- Mean CI Symptom Survey score less than 16
- AND
- Near point of convergence less than 6 cm
- AND
- Positive fusional vergence at near (i.e. greater than 15Δ and passing Sheard's criterion i.e., positive fusional vergence is at least twice the near phoria).

Improved is defined as

- Mean CI Symptom Survey less than 16 or a decrease in CI Symptom Survey from eligibility to the 12-week masked examination of more than 10 points
- AND
- Near point convergence less than 6 cm or a decrease in NPC from eligibility to the 12-week masked examination of more than 4 cm
- OR
- Normal positive fusional vergence (i.e., greater than 15Δ and passing Sheard's criterion i.e., positive fusional vergence is at least twice the near phoria) or an increase in PFV from eligibility to the 12-week masked examination of more than 10Δ

A subject is classified as a non-responder if he/she does not fall into either of the previous classifications.

Comparison of these percentages will be performed using polychotomous logistic regression analysis. This analysis technique will also allow for the inclusion of demographic and/or clinical measures from the eligibility examination that are thought to affect the probability of a subject being classified into one of the three categories.

Analysis of long-term follow-up data

All subjects will be asked to return for follow-up masked examinations at 6 and 12 months after completion of the 12-week primary outcome examination. Subjects who were asymptomatic at week 12 will be asked to perform maintenance therapy until returning for the 6-month examination and no therapy thereafter. On the other hand, symptomatic subjects will be referred to a non-CITT clinician to discuss alternative treatment options. In addition, any asymptomatic subject who scores ≥ 16 on the symptom survey at the follow-up examinations will be offered an alternative treatment. As such, the data from the 6- and 12-month examinations can be assumed to come from an observational study of CI treatments. A repeated measures analysis of covariance will be used to compare the mean CI symptom survey score, near point of convergence and positive fusional vergence between treatment groups. Factors in the model will include treatment group (number of levels determined by the number of different treatment options used by symptomatic subjects) and time. Covariates included in the model will include the corresponding outcome measure obtained at the 12-week masked examination, the original

treatment group assignment and any identified confounders. To be included as a confounder, the variable must be related to outcome and treatment group. Interactions between treatment group and all covariates will be investigated if cell sizes permit.

All data analyses will be performed using the SAS software system. Unless specifically stated otherwise, an α -level of 0.05 will be used (i.e., p-values less than 0.05 will be considered significant).

2.9 Human Subjects Considerations

2.9.1. Human Subjects Approval

Human subjects' approval will be obtained by each clinic site to allow participation in the proposed clinical trial, including randomization and treatment. The consent forms for eligibility testing and study participation will be approved by the clinic site's Institutional Review Board (IRB).

Each clinic principal investigator is responsible for obtaining approval of his/her clinic site's consent and assent forms and approval for conducting the CITT from his/her local Institutional Review Board (IRB). Sample informed consent and assent forms are located in the Appendix of Chapters 5 & 6. A copy of each clinic's approved consent form and documentation of approval must be submitted to the Data Coordinating Center before subjects can be enrolled in the CITT. Each year, the Data Coordinating Center will send each site a reminder two months prior to the annual expiration date so that the continuing review can be completed in a timely fashion and the site's Human Subjects' approval will not expire. Documentation of IRB approval for the continuing review must be submitted to the DCC each year. In the event that a CITT subject needs to be seen in a clinic site other than the one he or she originally enrolled at, the subject will need to sign an informed consent at the clinic at which he or she is to be seen. The Data and Safety Monitoring Committee and the CITT Executive Committee will review consent/assent forms periodically to assure adherence to these standards.

2.9.1.1 Human Subjects Involvement and Characteristics

We intend to enroll a minimum of 25 subjects per site with symptomatic CI between the ages of 9 to <18 years. Children are included as they are the group of individuals who are most commonly treated for CI. Children less than 9 years are not included because of their limited ability to respond reliably to subjective testing and treatment procedures. Subjects with constant strabismus, amblyopia, eye disease, developmental disabilities, a history of head trauma, or systemic or neurological conditions that could potentially affect vergence (e.g., cerebral palsy, Down's syndrome, etc.) will not be eligible.

2.9.1.2 Sources of Materials

Research material for this study includes subject data collected from all subjects tested for eligibility. The data will be collected specifically for the purpose of this clinical trial. All study

procedures are similar to those conducted during routine testing and treatment for CI. Each subject will have a visit to determine eligibility, an initial training visit and if enrolled, either 1) 9 phone appointments and 3 follow-up office visits if assigned to Home-based Pencil Push-up therapy or Home-based Pencil Push-ups with Computer VT/Orthoptics or 2) 12 office visits if assigned to Office-based VT/Orthoptics or Office-based Placebo VT/Orthoptics. This includes masked examinations at the 4-, 8-, and 12-week office visits. Subjects who are considered to have achieved symptomatic relief at the end of 12 weeks will be assigned maintenance therapy to perform until the 6- month follow-up examination. Subjects who do not receive symptomatic relief at the end of the 12-week treatment program will be offered an alternative treatment from a non-CITT doctor. Long-term follow-up will be assessed at 6- month and 12- month after the completion of active treatment.

2.9.1.3 Potential Risks

The risks are the same for this study as they would be for non-participating subjects receiving VT/Orthoptics or pencil push-up treatment. Risks include a potential temporary increase in symptoms such eye discomfort, eyestrain, mild to moderate headaches, blurred vision, intermittent or transient diplopia, sleepiness, difficulty concentrating, movement of print and loss of comprehension of read material after short periods of time. Time lost during non-productive treatment may also be included. The likelihood that these potential side effects would be severe is minimal. It is not anticipated that these symptoms would occur any more often within the constraints of the CITT than they would in the context of the same care obtained outside the CITT. Alternative forms of treatment for CI are: (1) prism glasses for reading and (2) no treatment. Neither has been shown to be as or more effective than the study treatments.

2.9.1.4 Protection against Risk Including Confidentiality

The potential risks are minimal and would be the same for a subject enrolled in a VT/Orthoptics program or receiving pencil push-up treatment outside of this study. Although the physical risks from this study are quite minimal, increases in symptoms such as headaches, eyestrain, and blurred vision will be monitored throughout the study. The potential symptoms that can occur after therapy are self-limiting and usually last only a short period of time. Over-the-counter headache remedies provide rapid relief from headaches and eyestrain. Because the primary outcome measure is a symptom survey, any significant increases in symptoms will be readily apparent to the Data Coordinating Center at the 4, 8, and 12-week follow-up visits. In addition, the therapist will make a general inquiry regarding whether the subject has encountered any ill effects from treatment at each treatment visit. Upon identifying any potential adverse event, the site's principal investigator must be summoned and he/ she will file the appropriate paperwork (Adverse Event form) if necessary. In the unlikely case that a subject experiences severe symptoms from one of the treatments, he/she would be allowed to discontinue the study if he/she wishes. If required, medical intervention is available from local physicians.

All enrolled subjects will be identified by a number assigned centrally by the Data Coordinating Center. Subject data will be secured, both at the clinical sites and the Data Coordinating Center, in a manner to protect subject confidentiality. Only the PI, site coordinator, and therapist will have access to the data. The informed consent document and HIPAA form will inform all

participants that their data will be sent to the Data Coordinating Center. The subject will be identified by his/her study ID number only on data transmitted to the Data Coordinating Center. Although results of the study will be presented at scientific meetings and reported in medical journals, at no time will any of the study participants be identified. The study will be monitored by the Data and Safety Monitoring Committee to ensure the safety of the participants.

2.9.1.5 Potential Benefits of the Proposed Research to the Subjects and Others

Subjects will receive a 12-week treatment program and any required equipment at no charge. This benefit could be worth as much as \$1500. Subjects who remain symptomatic at the end of the treatment program will be offered an alternative treatment at no cost. As the risks of the study are very minimal and only include self-limiting asthenopic type symptoms, the potential benefits greatly outweigh the risks.

The proposed trial is the first time commonly prescribed treatments for CI will be rigorously evaluated. The results of this study will have a direct bearing on the future care that will be offered to 9 to <18 year old children who develop CI following the completion of the study. If Home-based Pencil Push-up treatment or Home-based Pencil Push-ups with Computer VT/Orthoptics is found to be more effective than Office-based VT/Orthoptics, this would result in a significant savings in terms of money and time for future subjects diagnosed with CI.

2.9.1.6 Importance of Knowledge to be Gained

Despite the prevalence of CI, the best treatment for CI is not known. This study will provide much needed information on the efficacy of pencil push-up therapy, pencil push-ups plus computer vision therapy/ orthoptics and vision therapy/ orthoptics treatment for CI. The proposed trial is also the first time that vision therapy/ orthoptics for any condition has been evaluated in a systematic manner. The results of this study will have a direct bearing on the future care that will be offered to children who develop CI following the completion of the study.

2.9.2. Inclusion of Women

Convergence insufficiency has no known predilection for males or females; therefore, we would expect that enrollment based on sex/gender would be evenly distributed. In the CITT Planning Grant, about 60% of the enrolled subjects in the 9 to <18 year old age group were female. Therefore, we expect the sex/gender distribution for the full-scale study to be similar. Enrollment of all eligible subjects, regardless of sex/gender will take place during the enrollment phase of the grant period. No specific outreach program will be needed in order to recruit eligible female subjects.

2.9.3. Inclusion of Minorities

We plan to recruit 208 subjects. The primary recruitment of subjects will be from the nine clinic sites. Potential subjects will be identified after routine vision examinations at these clinics, through referrals from area eye care practitioners and through advertising. Table 2-1 illustrates our sample demographics during the CITT pilot study for children 9 to < 18 years old.

Convergence insufficiency has no known predilection for any racial/ethnic background. Subjects of all racial/ethnic backgrounds will be recruited into the CITT without bias. The study chair and Executive Committee have selected clinic sites to ensure sufficient recruitment of minorities. During the CITT Planning Grant, almost 55% of enrolled subjects were minorities. We have added additional sites in San Diego, CA; Rochester, MN; Ft. Lauderdale and Miami, FL; and Birmingham, AL. We expect to recruit a large number of African-American subjects in Philadelphia and Birmingham, and a large number of Hispanic subjects in Miami and San Diego.

Although we anticipate enrolling a strong minority representation, we do not anticipate sex/gender and/or race/ethnicity differences in the intervention effect. However, the Data Coordinating Center will conduct valid analyses to detect any potential differences in intervention effect among sex/gender and/or racial/ethnic subgroups. Reports from the Data Coordinating Center to the Data and Safety Monitoring Committee (DSMC) will include analyses of the distribution of demographic factors (age, race, and gender) by clinic. Adjustments in recruitment practices by either individual clinics or by the entire study group will be made if necessary.

Table 2-1 Comparing Treatment Groups with Respect to Sample Demographics, 9 to <18 Year Olds

Characteristic	Pencil Push Ups	VT/Orthoptics	Placebo VT/Orthoptics	p-value
Mean Age (SD)	12.5 (2.6)	10.9 (2.0)	11.1 (1.6)	.091
Gender				.147
% Male	46.7	23.5	57.1	
% Female	53.3	76.5	42.9	
Race				.995
% White	33.3	35.3	33.3	
% African American	46.7	52.9	53.3	
% Hispanic	6.7	5.9	0.0	
% Other	13.3	5.9	13.3	

2.9.4 Inclusion of Children

We plan to recruit a minimum of 208 subjects between the ages of 9 to <18 years. Children are included as they are the group of individuals who are most commonly treated for CI. Children less than 9 years are not included because of their limited ability to respond reliably to subjective testing and treatment procedures. Based on the CITT group's recruiting experience from the CITT Planning Grant phase, children were easier to recruit than adults. We reached our recruitment goal in 9 months for children versus 14 months for the adults 19 to 30 years old. Therefore, we have no concerns regarding the recruitment of children for this study. All participating clinic sites have investigators who are experienced in the care of children's vision problems. Furthermore, the facilities at each clinic site are appropriate for examining and treating children. In addition to parental consent, written assent will be obtained from children who enroll in the study.

2.10 Data and Safety Monitoring Plan

The CITT full scale trial has developed a system for the appropriate oversight and monitoring of the conduct of the clinical trial to ensure the safety of all CITT participants and the validity and integrity of the CITT data.

2.10.1 Oversight of Monitoring

The Data and Safety Monitoring Committee (DSMC) will be responsible for monitoring all aspects of the trial, including monitoring statistical analyses of study data for evidence of harmful, beneficial or no treatment effects. This committee will insure that the data and safety monitoring plans are in place for the CITT and that the quality of these monitoring activities is appropriate for the CITT. The relationship of the DSMC, the Study Chair, and the Data Coordinating Center will be an interactive one with each proposing agenda items, data displays to be included in interim reports, statistical monitoring, and other guidelines. Only the DSMC and NEI representatives are provided with evidence of treatment effects while the study is still in progress. Any recommendation for a protocol change, based on accumulated data, will be forwarded to the CITT Executive Committee for implementation. The DSMC will meet to review reports prepared by the Data Coordinating Center. The first DSMC meeting occurred March 24, 2005 before recruitment began. The second such meeting will occur during the 14th month of the study when recruitment is just underway. The 3rd meeting is slated to occur during the 18th month when approximately one-half of the required 208 subjects will have completed the study. The fourth DSMC meeting will occur during the 30th month of the study when most of the 208 subjects will have completed the active treatment portion of the study. Another meeting will occur at about month 42 when all subjects will have completed the 6 month follow-up. Additional meetings may be scheduled at the request of any member of the DSMC because he or she has concerns regarding data contained in an interim report. The Study Chair and Data Coordinating Center personnel will help facilitate and coordinate the activities of the DSMC.

2.10.2 Composition of the DSMC

The voting members of the DSMC will not otherwise be involved in the CITT and will include clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about CI. For the clinicians we suggest a pediatric ophthalmologist with a background in orthoptics and an optometrist with expertise in binocular vision and vision therapy. The CITT Study Chair will require a policy that insures that DSMC participants do not have conflicts of interests with or financial stakes in the research outcome. The Director of the National Eye Institute will appoint the voting members with input from the CITT Executive Committee. In addition to the voting members, the DSMC will also include non-voting members who serve by virtue of their roles in the Study. These are:

- Study Chair
- Representative of the Data Coordinating Center
- National Eye Institute Project Officer

The Chair of the DSMC may invite other individuals to attend one or more meetings in order to advise the committee on the study design and procedures when necessary for proper interpretation of the data.

2.10.3 Performance/Meetings of the DSMC

The DSMC will meet first in open session; attended by the Study Chair, Data Coordinating Center Representatives, and other selected trial investigators as well as the NEI program staff or project officers. A closed session will then occur where the DSMC reviews the emerging study data. When "masked" data are presented or discussed, no masked investigators will be allowed to attend.

The DSMC and all study investigators must maintain confidentiality during all phases of the CITT including monitoring, preparation of interim results, review, and response to monitoring recommendations. Besides selected NEI program staff, other key NEI staff, and CITT Data Coordinating Center biostatisticians, only voting members of the DSMC will be allowed to see interim analyses of outcome data. Exceptions may be made under circumstances where there are serious adverse events, or whenever the DSMC deems it appropriate.