CONGENITAL ESOTROPIA OBSERVATIONAL STUDY (CEOS)
PROTOCOL

1. Objective:

To observe the early course of congenital esotropia in order to determine the probability of spontaneous resolution and to try to correlate this finding with various aspects of the esotropia such as the (1) size of the esotropia, (2) variability, and (3) presence of hyperopia.

2. Patient Eligibility

Patients meeting the following criteria are eligible for CEOS.

1) age between 9 and 17 weeks (63-119 days)
2) gestational age $\geq$ 37 weeks and birth weight > 2000 grams (4 lbs, 6 oz)
3) neurologically and developmentally normal as judged by the investigator's standard routine
4) esotropia $\geq$ 20 pd
   - no limitation of abduction consistent with Duane's Syndrome, 6th nerve palsy, restrictive myopathy, or other syndrome (limitation of abduction due to cross fixation is acceptable)
   - deviation may be variable or intermittent as long as esotropia is unequivocal
5) no nystagmus or head bobbing visible to the naked eye present in the primary position, including manifest latent nystagmus
6) no botulinum injections, extraocular muscle surgery, intraocular surgery previously performed and no plans to perform surgery prior to 28 weeks (196 days) of age
7) no prior treatment for amblyopia or spectacle correction for refractive error
8) no media opacities, structural ocular anomalies in the posterior segment, optic atrophy, or other ocular disorders that may be affecting vision

3. Examination Procedures

1) Historical information: in addition to the information required to assess eligibility (see above), the age that the esotropia was first noted will be recorded.
2) Visual assessment including an assessment of amblyopia
   - If the patient does not spontaneously alternate fixation, then to diagnose "no amblyopia" it is necessary that when the fixing eye is covered, the fellow eye must hold fixation either through a blink, for at least five seconds, or for a smooth pursuit movement.
3) Measurement of the esotropia and assessment of motility
   - The comitancy and completeness of abduction will be assessed. The presence of inferior oblique overaction, dissociated vertical deviation, and latent nystagmus (as routinely diagnosed by the examiner) will be recorded.
   - Ocular alignment is evaluated by a cover-uncover test to verify the presence of the esotropia and measured at near when possible with an alternate prism cover test (APCT) using an accommodative target. If this is not possible, then the deviation is measured using the Krimsky method with an accommodative target.
4) Cycloplegic retinoscopic refraction
   - Cyclopentolate 0.5% will be placed in each eye to achieve cycloplegia. Use of additional drops to increase pupil dilation is at the discretion of the investigator. The cycloplegic refraction will be performed 30 to 50 minutes after instillation of the drops. The refraction will be performed according to the investigator's usual routine.

5) Ocular examination including pupil dilation performed according to the investigator's usual routine.

4. Enrollment

For eligible patients, the purpose of the study and the protocol will be discussed with the infant's parent or guardian who will be asked to sign the informed consent form and provide the contact information requested on the Contact Information Form.

The steps to be followed to enroll an eligible patient are as follows:

1) Complete CEOS Enrollment Form and verify patient eligibility
2) Have informed consent form explained to parent or guardian by the investigator and then signed.
3) Complete Contact Information Form
4) Enter patient information onto the CEOS Patient Log in the front of the CEOS Master Binder and assign the patient the next ID number. Enter this number onto the Enrollment Form and Contact Information Form
5) Fax to the DCC or enter on the Internet the CEOS Enrollment Form
6) Place the Enrollment Form, Contact Information Form, and Informed Consent Form into the CEOS Master Binder behind the next unused tab and write the patient's ID number and name on the tab.

5. Diagnosis and Treatment of Amblyopia and Refractive Error

Ambylopia and refractive error are to be treated according to the investigator's usual routine.

6. Follow-up Examinations

All patients are required to have two examinations in addition to the enrollment examination: (1) 2-4 weeks (14-28 days) after the enrollment examination but no later than 19 weeks (133 days) of age and (2) between 28 and 32 weeks (196-224 days) of age. These examinations will be similar to the enrollment exam described in section 3, with the exception that a repeat refraction and posterior segment examination with pupil dilation are not required. If spectacles were prescribed at an earlier visit, measurements of the esotropia will be made with and without correction.

Additional examinations should be performed according to the investigator's usual routine. Data will be submitted to the DCC for all examinations performed prior to strabismus surgery or 12-months of age whichever comes first.

7. Sample Size

The sample size for the CEOS will be 150 patients, with at least 100 patients having a constant esotropia at the enrollment visit $\geq$40 pd and <3.00D of hyperopia (current ESCET eligibility criteria). The table below gives the upper limits of one-sided and two-sided 95% confidence intervals for a sample size of 100 if 0, 1, or 2 cases of spontaneous resolution are found among the patients meeting current ESCET eligibility criteria.

	Upper limit of 95% CI for N=100	
# of cases of spontaneous resolution	1-sided	2-sided
0	3.0%	3.6%
1	4.7%	5.4%
2	6.2%	7.0%
3	7.6%	8.5%
4	8.9%	9.9%
5	10.2%	11.3%

Our best guess based on current knowledge is that there will be 0 or 1 case of spontaneous resolution among the 100 patients meeting ESCET eligibility criteria.

8. Data Analysis and Publication

For each patient the change in the angle of the esotropia from the enrollment examination to the 28-32 week examination will be determined. The distribution of the change scores will be reported overall and also stratified by size of the esotropia at enrollment, age at enrollment, refractive error and treatment for amblyopia. In each stratum, the proportion of patients whose esotropia spontaneously resolved will be determined. A second approach will be to assess the patients whose esotropia resolved as a group to determine whether there are any common features that distinguish these cases from the ones that did not resolve.

A manuscript with group authorship will be written with the results of the CEOS. All investigators who enroll and complete follow up on at least one patient will be listed in the manuscript. A presentation of the results will be made at a national ophthalmology or pediatric ophthalmology meeting.

9.Data Coordinating Procedures

The DCC will establish a password-protected database on its Internet web site to allow for data entry (isolated from Jaeb computer network for security purposes). It also will accept faxing of forms. A communication will be sent to the investigator each time a form is received.

The DCC will send the investigator a reminder when a 28-32 week visit is pending and will contact the investigator when week 32 has passed without a form being submitted to the DCC.

For patients who miss the 28-32 week visit, the DCC will work with the clinical investigator to try to locate the patient/family. If the patient/family has moved or is unwilling to return to the investigator's office, an attempt will be made to coordinate an examination with another ophthalmologist.