AMBLYOPIA TREATMENT STUDY 20
Binocular Dig Rush Game Treatment of Amblyopia
(Protocol version 3.1: 03-07-18)

ELIGIBILITY CRITERIA

The following criteria must be met for the patient to be enrolled in the study:

1. Age 4 to <13 years
2. Amblyopia associated with strabismus, anisometropia, or both (Previously treated or untreated)

a. Criteria for strabismus: At least **one** of the following must be met:

- Presence of a heterotropia on examination at distance or near fixation (with or without optical correction), must be no more than 4pd by SPCT at near fixation.
- Documented history of strabismus which is no longer present

b. Criteria for anisometropia: At least **one** of the following criteria must be met:

- ≥1.00 D difference between eyes in spherical equivalent
- ≥1.50 D difference in astigmatism between corresponding meridians in the two eyes

c. Criteria for combined-mechanism amblyopia: **Both** of the following criteria must be met:

- Criteria for strabismus are met (see above)
- ≥1.00 D difference between eyes in spherical equivalent OR ≥1.50 D difference in astigmatism between corresponding meridians in the two eyes

3. No amblyopia treatment in the past 2 weeks (patching, atropine, Bangerter, vision therapy, binocular treatment)
4. Requirements for required refractive error correction (*based on a cycloplegic refraction (CR) within the last 7 months old*):

- Hypermetropia of 2.50D or more by spherical equivalent (SE)
- Myopia of amblyopic eye of 0.50D or more SE
- Astigmatism of 1.00D or more
- Anisometropia of more than 0.50D SE

Note: Subjects with cycloplegic refractive errors that do not fall within the requirements above for spectacle correction may be given spectacles at investigator discretion but must follow the study-specified prescribing guidelines, as detailed below.

a. Spectacle prescribing instructions referenced to the CR completed within the last 7 months:

- SE must be within 0.50D of fully correcting the anisometropia.
- SE must not be under corrected by more than 1.50D SE, and reduction in plus sphere must be symmetric in the two eyes.
- Cylinder power in both eyes must be within 0.50D of fully correcting the astigmatism.
- Cylinder axis must be within +/- 10 degrees if cylinder power is ≤1.00D, and within +/- 5 degrees if cylinder power is >1.00D.
- Myopia must not be under-corrected by more than 0.25D or over corrected by more than 0.50D SE, and any change must be symmetrical in the two eyes.

b. Spectacle correction meeting the above criteria must be worn:

- 16 weeks ***OR*** until VA stability is documented (defined as <0.1 logMAR change by the same testing method measured on 2 consecutive exams at least 8 weeks apart).
  - Determining visual acuity stability (non-improvement):
    - The first of two measurements may be made **1)** in current correction, or **2)** in trial frames with or without cycloplegia or **3)** without correction (if new correction is prescribed),
    - The second measurement must be made without cycloplegia in the correct spectacles that have been worn for at least 8 weeks.
    - *Note: since this determination is a pre-study procedure, the method of measuring visual acuity is not mandated.*

5. Visual acuity, measured in each eye without cycloplegia in current spectacle correction (if applicable) within 7 days prior to randomization using the ATS-HOTV VA protocol for children < 7 years and the E-ETDRS VA protocol for children ≥ 7 years on a study-approved device displaying single surrounded optotypes, as follows:
   a. VA in the amblyopic eye 20/40 to 20/200 inclusive (ATS-HOTV) or 33 to 72 letters (E-ETDRS)
   b. Best-corrected fellow-eye VA meeting the following criteria:
      - If age 4, 20/40 or better by ATS-HOTV
      - If age 5 or 6, 20/32 or better by ATS-HOTV
      - If age 7 or older, 20/25 or better by E-ETDRS (≥78 letters).
   c. IOD ≥ 3 logMAR lines (ATS-HOTV) or ≥ 15 letters (E-ETDRS)
6. Heterotropia with a near deviation of < 5Δ (measured by SPCT) in habitual correction
7. Subject is able to play the Dig Rush game (at least level 3) on the study iPad under binocular conditions (with red-green glasses). Subject must be able to see both the red "diggers" and blue "gold carts" when contrast is at 20% for the non-amblyopic eye.
8. Investigator is willing to prescribe computer game play, or continue spectacle wear per protocol.
9. Parent understands the protocol and is willing to accept randomization.
10. Parent has phone (or access to phone) and is willing to be contacted by Jaeb Center staff or other study staff.
11. Relocation outside of area of an active PEDIG site for this study within the next 8 weeks is not anticipated.

EXCLUSION CRITERIA

1. Prism in the spectacle correction at time of enrollment (eligible only if prism is discontinued 2 weeks prior to enrollment).
2. Myopia greater than -6.00D spherical equivalent in either eye.
3. Previous intraocular or refractive surgery.
4. Any treatment for amblyopia (patching, atropine, Bangerter filter, or previous binocular treatment) during the past 2 weeks. Previous amblyopia therapy is allowed regardless of type, but must be discontinued at least 2 weeks prior to enrollment.
5. Ocular co-morbidity that may reduce VA determined by an ocular examination performed within the past 7 months (*Note: nystagmus per se does not exclude the subject if the above visual acuity criteria are met*).
6. No Down syndrome or cerebral palsy
7. No severe developmental delay that would interfere with treatment or evaluation (in the opinion of the investigator). Subjects with mild speech delay or reading and/or learning disabilities are not excluded.
8. Subject has demonstrated previous low compliance with binocular treatment and/or spectacle treatment (as assessed by investigator)

ENROLLMENT/RANDOMIZATION PROCEDURES

All examination procedures must be tested within 7 days prior to the date of enrollment, except the cycloplegic refraction and ocular examination, which may be performed within 7 months prior to enrollment.

All examination procedures at enrollment are performed in the subject's current spectacle correction, if required (testing in trial frames is not permitted) and without cycloplegia:

1. ATS Diplopia Questionnaire
   The child and parent(s) will be specifically questioned regarding the presence and frequency of any diplopia within the last 2 weeks using a standardized diplopia assessment (*see ATS Misc. Testing Procedures Manual*). The diplopia assessment must be performed prior to any other testing during the exam.
2. Symptom Survey
   The child and parent(s) will complete a 5-item symptom survey regarding the presence of various ocular symptoms within the past 2 weeks (*see ATS Misc. Testing Procedures Manual*). The symptom survey must be performed prior to any other testing during the exam.
3. Distance VA Testing
   Monocular distance VA testing will be performed in current refractive correction (if required) in each eye by a certified examiner using the electronic ATS-HOTV VA protocol for children <7 years and the E-ETDRS VA protocol for children ≥7 years on a study—certified acuity tester displaying single surrounded optotypes as described in the *ATS Testing Procedures Manual*.
   - **The same VA protocol used at enrollment will be used throughout the study regardless of age at follow-up.**
4. Stereoacuity Testing
   Stereoacuity will be tested at near in current spectacle correction using the Randot Butterfly and Randot Preschool stereoacuity tests.
5. Ocular Alignment Testing
   Ocular alignment will be assessed in current spectacle correction by the cover test, simultaneous prism and cover test (SPCT) (in cases of strabismus detected by cover test), and prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and at near (1/3 meter) as outlined in the *ATS Procedures Manual*.
6. Additional Clinical Testing
   Ocular examination as per investigator's clinical routine (if not performed within 7 months)
7. Demonstration of Game Understanding
   Subject must be able to see both the red "diggers" and blue "gold carts" when contrast is at 20% for the non-amblyopic eye. Subjects must demonstrate that they understand the game by playing the game in the office on at least level 3. Subjects unable to play the game are not eligible for the study.

RANDOMIZED TREATMENT GROUPS

Subjects will be randomly assigned to one of the following treatment groups for 8 weeks:

- **Binocular game play**: binocular Dig Rush game prescribed 1 hour per day, 5 days per week (treatment can be split into shorter sessions totaling 1 hour per day)
- **Continued spectacle correction**: subjects will continue to wear their appropriate spectacle correction (if required) for all waking hours, 7 days per week.

SUMMARY OF TESTING PROCEDURES

	Baseline	*1 week*	*4 weeks ± 1 week (Primary Outcome)*	*8 weeks ± 1 week (Secondary Outcome)*	*9 weeks**	*16 weeks ± 1 week**
Telephone call		**X**			**X**	
Diplopia Questionnaire	**X**		**X**	**X**		**X**
Symptom Survey	**X**		**X**	**X**		**X**
Monocular Distance VA	**X**		**ME**	**ME**		**X**
Randot Stereoacuity (Butterfly & Preschool)	**X**		**ME**	**ME**		**X**
Cover/Uncover Test, SPCT, PACT	**X**		**X**	**X**		**X**

ME refers to testing by an examiner who is masked to the patient's treatment group.

* Only for group originally randomized to continued spectacle treatment who opt to receive binocular treatment at the 8-week visit