Boston Children's Hospital

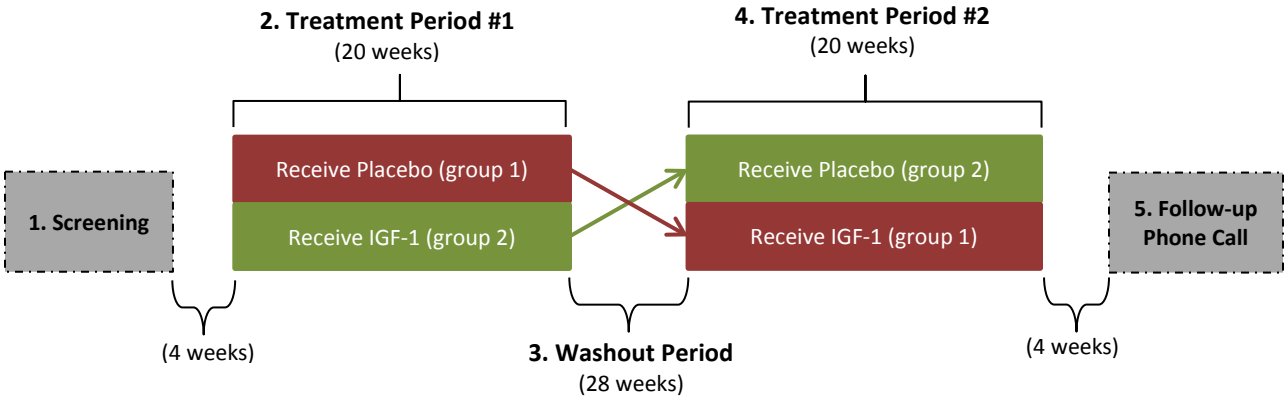
Phase 2 Clinical Trial for the Treatment of Rett Syndrome with IGF-1

The Rett Syndrome Research Program at Boston Children's Hospital (BCH) is recruiting subjects for the Phase 2 clinical trial entitled "Pharmacological Treatment of Rett Syndrome by Stimulation of Synaptic Maturation with IGF-1". Please continue reading to learn more about the study and how your child may participate.

This Phase 2 trial will include 30 children with Rett syndrome who are female, between the ages of 2 to 10 years old (up to 10 years 11 months), have a clinical diagnosis of "Classic" or "Typical" Rett syndrome, have a documented genetic *MECP2* mutation, demonstrate a specific behavioral profile (based on standardized questionnaires), reside within North America (USA and Canada) and whose primary language (language most commonly spoken at home) is English. Subjects must also be in a "stable" stage of the disease; i.e. no longer experiencing symptoms or signs of regression (loss of skill). Study participants must be stable on their regimen of medications for 4 weeks prior to beginning the study. If receiving services (such as physical, occupational, or speech therapy), subjects must be on a stable regimen of these services for 90 days prior to initiating treatment with study drug. Additionally, study participants' caregivers must have access to the internet and be able to complete questionnaires online and correspond via email. During the screening visit in the hospital, a study doctor will determine eligibility and ensure each child is healthy enough to participate in the trial.

Phase 2 is a double-blinded, placebo-controlled cross-over study designed to test the efficacy of IGF-1. Children enrolled in the study will go through five "study periods":

1. Screening period (includes "pre-screening" of parent-completed materials),
2. The first 20-week treatment period,
3. A 28-week "washout" period (no drug treatment),
4. The second 20-week treatment period,
5. And a follow-up phone call 4 weeks after treatment ends.



Subjects will be chosen at random to receive either IGF-1 or placebo during the first treatment period and then switch to the alternate medication for the second treatment period. Therefore, by completion of the trial, all girls will have received treatment with IGF-1 for 20 weeks. The study will be double-blinded; meaning, neither subjects' families nor study investigators will know who is receiving IGF-1 or placebo at any time. Treatment must be administered by the caregiver twice daily through subcutaneous (just underneath the skin) injections. Caregivers will be trained by research nurses in how to administer the medication. Participation in this study will last approximately 18 months.

Throughout the course of the trial, we will collect information to assess the effects of IGF-1 and monitor for safety. Families must attend study visits at BCH at the beginning, middle and end of each treatment period (total of 6 visits). These visits cannot be completed at any other hospital. Parents will fill out questionnaires and undergo a structured interview reporting on their child's health, behavior, and mood. Subjects will undergo

clinical and physical examinations by a study doctor. Non-invasive devices and cameras will also be used to monitor things like breathing, hand movements, heart rate, and body temperature. Blood and urine will be collected for routine laboratory tests to monitor for safety. Investigators will also monitor safety by asking parents to complete a medication diary and side effect reporting form on a regular basis. Between trips to BCH, parents will complete a set of online questionnaires and undergo a structured interview over the phone.

The cost of travel and lodging during research-related visits to and from the hospital will not be covered by the study. However, there are several hospital-sponsored low cost lodging options located within walking distance to the hospital which are made available for children undergoing treatment at BCH. If a condition or illness is identified during the trial, referrals to outside medical care will be made. Study medications and all research-related materials and services will be provided at no cost to participants. Parking vouchers will be provided for all study-related hospital visits.

If at the end of the study, you would like your child to continue treatment with IGF-1, we will refer her to the Department of Endocrinology for a clinical evaluation. Your child will be seen by an endocrinologist that is experienced in managing the ongoing care of children treated with IGF-1 and is familiar with Rett syndrome.

If you would like your child to be considered for participation in the IGF-1 trial, please complete and return the pre-screening packet attached to this correspondence. This packet includes the following forms:

1. Study intake form
2. Developmental and medical history form
3. Current and previous medication logs
4. Rett Syndrome Behavioral Questionnaire (RSBQ)
5. Anxiety, Depression and Mood Scale (ADAMS)

In addition to the aforementioned documents, please include the following records with your submission:

1. Copy of genetic test results demonstrating a *MECP2* mutation
2. Growth charts from birth to 2 years old, including head circumference (also called 'FOC' or 'HC')

You may submit these materials via email to rettresearch@childrens.harvard.edu or via fax to 617-730-4669. You may also submit printed copies by standard mail to the following address:

Rett Syndrome Research Program
c/o Boston Children's Hospital
1 Autumn Street, Box #26
Boston, MA 02215

Please note: Submission of pre-screening materials does <u>not</u> automatically enroll your child in the trial.

Investigators will review this information as part of the pre-screening process to determine if your child is eligible for the trial. You will be contacted if we require further information or if we would like to schedule an in-person screening visit at Boston Children's Hospital. Investigators will need time to review laboratory results from blood and urine collected during the screening visit before final eligibility can be determined. If your child is eligible, you will be notified as soon as possible.

If you have sent us screening information about your child for the IGF-1 trial in the past, we thank you. However, because many forms have changed and previously submitted information may no longer be current, we ask that you please **<u>submit all screening materials again</u>.** If you have any questions or concerns about the trial please contact our office at rettresearch@childrens.harvard.edu or 617-355-5230.

Thank you,
The Rett Syndrome Research Program
Boston Children's Hospital