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To: Karim Calis, Pharm.D., MPH, IRB Chair, NICHD IRB

Recommended by:

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Project Title: Studies of Growth Deficiency and Growth Hormone Treatment in Children with Osteogenesis Imperfecta Types III and IV

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Estimated Duration of Study: 20 years

Total Patients to be Recruited: 60

Normal Volunteers: None

Description of Patient Population: Children with Osteogenesis Imperfecta (Types III and IV), and short stature, ages 3 through 15 years.

PRECIS:

Growth deficiency is a cardinal feature of severe Osteogenesis Imperfecta (OI) and a frequent feature of mild to moderate forms of this disease. Despite the prevalence of short stature among people with OI, few studies have examined treatment options for this feature of OI. Recombinant human growth hormone (rGH) is a treatment for growth deficiency which we have investigated. In our initial studies we have found that many OI children are responsive to rGH, especially those with type IV OI. The purpose of this protocol is to examine the effect of growth hormone treatment on linear growth of children with types III and IV OI and correlate growth responsiveness with growth hormone-somatomedin axis and histomorphometry parameters of OI bone.

INTRODUCTION:

Osteogenesis Imperfecta (OI) is a heritable disorder of connective tissue with bone fragility as the hallmark feature. Classical autosomal dominant OI is caused by structural defects in the genes coding for type I collagen (*COL1A1* and *COL1A2*). [1] Growth deficiency is the most striking secondary feature of OI. Severe growth deficiency is always present in type III OI and is a frequent feature of moderate (type IV) OI. In general, the degree of growth deficiency parallels the severity of the bone disease in morphologic and radiographic features but not in fracture number. [2]

Typical growth patterns have been defined **for** classical autosomal dominant OI types. Many of these children are small to normal size at birth, but virtually all Types III and IV patients begin to plateau in length beginning about 12 months. This continues through about age 4 years for Type IV, when most of these children begin to grow at normal growth rates, but below the lowest percentiles of the standard growth chart curve. It is possible that Type IV children could have normal stature if the plateau phase were eliminated. Type III children tend to demonstrate only small growth gains. [3] The reasons for this plateau phase are unknown. The National Institute of Child Health and Development (NICHD) has produced data addressing growth deficiency in older OI children, but there have been no efforts to date focused on the plateau phase in early childhood. [4]

At a molecular level, autosomal dominant osteogenesis imperfecta is associated with defects in either of the two chains which comprise type I collagen. [5] Type I collagen is a heterotrimer, made up of two $\alpha 1$ chains and one $\alpha 2$ chain, which constitutes the most abundant protein in bone, skin, and tendon. Inadequate amounts or abnormal forms of type I collagen can account for the matrix abnormalities, osteoporosis and bone fragility of OI. [6] The role of skeletal matrix abnormalities in short stature is unclear. Possible roles include unresponsiveness of the target tissue to local and systemic growth factors or abnormal feedback of target tissue on the endocrine axis.

There is now considerable data available on normal growth markers in children. At the research level of investigation, unstimulated 12 and 24 hour growth hormone sampling and somatomedin generation testing have become routine in the evaluation of growth in children. [7] Dr. Rose has also produced data on unstimulated 6 hour growth hormone sampling. She has found that the 6 hour sampling corresponds to the 12 hour results. [8] The data most applicable to our population of 1-5 years of age were determined in pre-pubertal children below the age of 8 years. Unless our results show marked inconsistencies, there is no reason not to consider this normative data comparable (S. Rose, personal communication). Markers of skeletal formation include osteocalcin, a bone specific protein made by osteoblasts, and procollagen peptide type I (PICP). Studies have shown that these markers correlate with age and puberty, reflecting higher levels during periods of maximum growth, and very low levels as puberty ends and during adulthood. [9]

Markers of bone turnover include bone specific alkaline phosphatase, IGF Binding Protein-3 (IGFBP-3), and Growth Hormone Binding Protein (GHBP). We have assessed these values in the children currently enrolled in the OI growth hormone study.. Specific normative data is available for bone specific alkaline phosphatase and IGFBP-3. IGFBP-3 normative data is available in 2-4 year ranges, beginning at birth. Recently bone specific alkaline phosphatase during childhood (i.e., 2 months to 18 years broken down to 2 year intervals) have been established. [10] In contrast, normative data about GHBP, which indirectly measures the circulating portion of the growth hormone receptor, is available but the age ranges are very broad, ages 3 to 10 years, and 10 to 15 years

We began investigating the status of hormones related to growth in 28 children with osteogenesis imperfecta. [11] This original investigation was prompted by the observation that several children with OI, who served as non-endocrine controls in GHD studies, did not have normal test results. Our goals were to determine 1. whether there were any abnormalities of the growth hormone / somatomedin-C axis in this condition, 2. whether any abnormalities correlated with the type of OI, and 3. whether OI bone could be safely stimulated to grow. The endocrine evaluation of the OI children included a GRF stimulation test, three standard GH provocative tests (Arginine-Insulin tolerance test, L-Dopa stimulation test), a 24 hour q 20 minute sampling for measuring basal, unstimulated concentrations of GH and a somatomedin generation test.

Endocrine evaluation of 28 patients at the NIH has shown that about half of them have a low area under the integrated curve of unstimulated 24 hour growth hormone secretion, and fail to respond positively to a growth hormone releasing hormone stimulation test or a somatomedin generation test. [12]

Complete evaluation of the hormonal axis related to growth in short children with OI revealed subtle deviations from normal in some of the children; there was no pattern of response to any test or among any sequence of tests that correlated with the type of OI or the degree of growth deficiency. The only significant correlation of test results was that 12 children, whose response to GRH was comparable to the GRH response of GHD children [13], had a significantly lower area under the 24 hour curve of unstimulated growth hormone secretion, while 14 children with a normal response to GRH also had a normal area under the 24 hour growth hormone secretion curve. Thus, one group appeared to have a relatively hypoactive growth hormone axis even though, by standard criteria of GH provocative tests and the 24 hour GH sampling, they did not fill the criteria of growth hormone deficiency.

Furthermore, the OI children as a group demonstrated a blunted response in the somatomedin generation test, with 21/28 children having a baseline IGF-I below the mean for age and 18/28 children having less than a two-fold stimulation in response to growth hormone injections. The group with blunted IGF-I response did not correlate with the low GRH-low 24 hour area group. This was not surprising since one would not expect relatively low growth hormone to be correlated with unresponsiveness of somatomedin to growth hormone stimulation. More problematic was the interpretation of IGF-I levels in children, whatever their height or bone morphology. IGF-I is known to be responsive to GH stimulation and is itself functionally defined in terms of its ability to stimulate

sulfation in bone. [14] Although the predominant quantity of IGF-I is made in the liver, it is also made in multiple other tissues including bone itself, where its synthesis has been localized to a region of the growth plate. [15] The tissue of origin of basal and GH-stimulated IGF-I is unmeasurable and so the functional significance of the test is difficult to assess. In a primary defect of bone matrix, even a successful stimulation of IGF-I level may not represent an effective functional increment in terms of growth stimulation.

The study of the growth response of OI bone to growth hormone also allowed us to address the effect of hormonal stimulation on the secondary consequences of abnormal bone matrix (collagen) by measurement of the histomorphometry of the bone. There is *in vitro* evidence demonstrating that growth hormone stimulates proliferation of osteoblasts and increases their production of collagen via IGF-I. [3] In the current protocol, we propose to examine iliac crest biopsies to determine if there is an effect of growth hormone on bone histomorphometric parameters apart from its effect on linear growth. Previous studies [4] on tetracycline-labeled iliac crest biopsies from OI children have demonstrated 1. decreased cancellous bone volume and trabecular thickness, 2. no evidence of increased resorption, 3. decreased synthesis of an organized matrix in type I OI (mild), 4. disorganized matrix in type III OI (severe), consisting of a mixture of lamellar and woven structure with irregular tetracycline labeling, and 5. poor organization of cortical bone in type III OI, often with absence of Haversian systems.

This protocol has produced some encouraging results for rGH treatment of OI children. We have treated 36 children, ages 5-12 years and including 14 type III and 22 type IV OI children. During the treatment trial, children receive 0.06mg/kg/day of Humatrope, 6 days per week for one year. Nineteen of the 36 children demonstrated a positive response to treatment. This responder group was composed predominantly of children with type IV OI; 13 of the responders have type IV OI and 70% of the treated type IV children were growth responders. [9] Overall, half of the treated children responded.

The only bone metabolic marker which differentiated responders from non-responders was procollagen peptide type I ($p=0.04$). Responders had higher PICP than non-responders at baseline and after 6 and 12 months of treatment. A cut-off PICP value of 86 mg/ml is 73% predictive of OI response to rGH.

The total patient group showed significant increases over baseline in IGF-I, IGFBP-3, Procollagen Peptide type I, and osteocalcin by 6 months of treatment. Bone specific alkaline phosphatase was significantly increased over baseline by one year. [9]

Bone histomorphometrics of responders show a significant increase in bone volume/total volume, mineralized bone volume/total volume and bone formation rate/total volume. [9]

Our interpretation of our results is that there is a significant population of OI children, especially with type IV OI, who respond to growth hormone treatment with increased growth rates and positive changes in bone formation.

OBJECTIVES:

- (1) To determine the range and duration of growth responsiveness of OI bone;
- (2) To determine the correlation of this growth responsiveness with the results of the endocrine evaluation of the growth hormone somatomedin axis;
- (3) To determine the effect of growth hormone on the density and histomorphometric parameters of OI bone;
- (4) To determine the long term benefits of this therapy for final stature, trunk length, and pulmonary function.

STUDY DESIGN AND METHODS:

PART A

PRE - TREATMENT YEAR AND EVALUATION OF HORMONAL STATUS

The pre-treatment interval will be a one year time period during which children will be serving as their own baseline controls. The visit schedule will be every 3 months. Linear growth on each side of the body will be measured at each visit with 5 lengths using a supine length board. Other measurements at each visit will include weight, arm span, sitting height, upper and lower extremity segments, and head circumference. At 6 month intervals, radiographic assessments of spine, and lower extremities will be performed, as well as bone density of the lumbar spine. Radiographic assessments of bone age will be done annually.

Children enrolled in this protocol will be co-enrolled in protocol 97-CH-0064 and will undergo pulmonary testing and neurological imaging on the schedule for that protocol. For pulmonary function testing, the tests will be completed at Children's National Medical Center. Children too young to cooperate with the procedures of pulmonary function testing will not be sedated for these procedures. Additionally, neuroimaging studies of the head and neck, including CT and MRI scan, will commence when the child is able to cooperate without needing sedation. In our experience, children age 4-5 years are able to hold still for the CT scan, which takes approximately 5-10 minutes. If signs of Basilar Invagination (BI) are detected, the children progress to having MRI scans every year.

An iliac crest bone biopsy will be obtained at the beginning of the treatment year for growth hormone. This biopsy will be repeated at the end of the growth hormone treatment year. The biopsies will be obtained by Dr. Bhattacharyya for analysis in Dr. Hefferan's laboratory. The procedure will be performed under general anesthesia in the operating room at the NIH.

During the pre-treatment year, the following testing will be done for endocrine evaluation.

1. Baseline CBC 1.5cc
2. Somatomedin Generation Test [14] 3.2 cc / draw (includes discard)
2.0 cc added to Baseline and Day 5
20.0 cc total

Our experience with this test in OI children shows that 89% demonstrate a peak response beginning at 48 hours after the initial injection. Therefore we plan to do the full 6 day test, but only draw blood at baseline (day 0) and days 2-5. To evaluate for the possibility of growth hormone resistance, we will measure GHBP and IGFBP-3 at baseline and day 5 of this test.

3. IGF-I 3.0 cc
IGFBP-3, GHBP
Bone Specific Alk Phos 6.0 cc
Osteocalcin, Type I Collagen Peptide 4.0 cc
TSH, FT₄, T₄ 4.0 cc
Glycosylated Hemoglobin 5.0 cc
Total 22.0 cc

These growth factors will be obtained at 6 month intervals.

4. 6 hour growth hormone sampling 1.7 cc/draw (inc. discard); 32.3 cc total
or
12 hour growth hormone sampling [17] 1.7 cc/draw (inc. discard); 62.9 cc total

The 6 hr testing will be used for patients with a minimum weight of 6.5 kg through 12.6 kg. The 12-hour evaluation will be done for children 12.7 kg or greater.

This endocrine testing will be spread out over the 3-month visit schedule to remain within the NIH guidelines for safe amounts of blood withdrawal from children. Scheduled visits will be inpatient on the 1 Northwest Pediatric unit when overnight serial blood testing or a bone biopsy is scheduled. Other scheduled visits will be outpatient day hospital visits.

VISIT	Meas	XR	BA	BMD	Growth Factors	SGT	Serial GH	CBC	Bone Biopsy	Pulm/Neuro
Baseline	X	LE, spine	X	X	X			X		Per 97-CH-0064
3 month	X					X				
6 month	X	LE, spine		X	X		X			
9 month	X									
12 month (baseline part B)	X	LE, spine	X	X	X			X	X	

PART B

GROWTH HORMONE TREATMENT

In this part of the protocol, OI children will be treated with synthetic growth hormone (Humatrope®, generously donated by Eli Lilly and Company) for one year to identify responders. Responders will be identified as those children who are able to achieve and sustain a 50% increase in growth rate over their baseline. Responders will be treated an additional 2 years. After the third year of treatment, responders will be defined as those children who demonstrate a sustained increase of 30% or greater from baseline. Children who are responders at the 3 year mark will be treated with growth hormone through final adult height. Final adult height will be defined as epiphyseal-metaphyseal union of the distal femur and proximal tibia growth plates. We will attempt to follow all participants through final adult height.

The planned visit schedule is every 3 months starting at the baseline period and continuing through treatment completion.

Parameters which will be followed during the treatment year will be a continuation of those followed during the pre-treatment year, and are summarized in the following table:

Visit	Measures	XR	Bone Age	Growth Factors	Bone Density	Bone Biopsy	Pulm/Neuro
PART B BASELINE (Rx year, also part A 12 mo visit)	X	X	X	X	X	X	Per 97-CH-0064
3 MONTH	X						
6 MONTH	X	X		X	X		
9 MONTH	X						
12 MONTH	X	X	X	X	X	X	
RESPONDERS 6 MONTH	X	X		X	X		
12 MONTH	X	X	X	X	X		
TREATMENT END, 3 YEAR NON-RESPONDERS	X	X	X	X	X		
ADULT STATURE	X	X	X	X	X		

All visits will be outpatient day hospital visits with the exception of those visits when a bone biopsy is scheduled.

MONITORING SUBJECTS, DOSAGE, AND CRITERIA FOR WITHDRAWAL OF SUBJECTS FROM THE STUDY

Treatment with Humatrope® will begin at the 12 month pretreatment visit/baseline treatment visit. The accompanying parent will learn how to reconstitute the drug and administer the subcutaneous injections. The dose will be 0.06 mg/kg/day for 6 days of the week. At the end of 12 months of treatment, those children who have responded with a

sustained 50% increase in growth rate will remain on Humatrope® injections for an additional 2 years. After the third year of treatment, responders will be defined as those children who demonstrate a sustained increase of 30% or greater above baseline. These responders will be treated through attainment of final adult height as defined above.

STRATIFICATION AND RANDOMIZATION

All patients entering this study will undergo the same protocol as described above. There will be no randomization.

HUMAN SUBJECTS PROTECTIONS

Children enrolled in this study will be limited to those with Sillence Types III and IV OI, as determined by clinical and genetic criteria. This disorder is autosomal dominant, and occurs with equal distribution in males and females. The disorder has been described in all races and has no ethnic preference. There are no exclusionary criteria related to race or gender for this protocol.

CRITERIA FOR PATIENT SELECTION

Patients will be recruited with the goal of including at least 10 each of individuals with clinical/biochemical criteria of types III and IV OI who are between 3 and 8 years of age.

1. Height: Individuals with type III OI have severe short stature by definition; individuals with type IV OI recruited to the study will have height less than the 3rd percentile for age. All individuals will be required to furnish growth records, especially height and head circumference, from at least the preceding two years.
2. Long bone status: Participants must have radiographic evidence that long bone epiphyses have not yet fused. In addition, 60° or greater angulation of a femur will exclude a child, pending surgical management or medical clearance.
3. Spine: Prospective participants will be evaluated for scoliosis and spinal compressions. Participants with scoliosis greater than 40° will be excluded unless evidence is presented that the scoliosis has been stable for the prior two years. Participants with corrective rods in their spine will be excluded.
4. Neuro status: All patients will be co-enrolled in 97-CH-0064, and will be screened for Basilar Invagination through that protocol. Children who are initially screened by spiral CT scan with MRI confirmation and determined to have severe BI will be excluded from participation in this study. Severe BI is defined by NIH data as distortion of the angle between the pons and medulla and or compression of posterior fossa contents. [18] We are only beginning to define the parameters of BI in this population, and we do not know why some children with BI progress in severity and some do not. Until those questions are answered, we feel it would not be prudent to stimulate growth in a child we know to have a severe form of BI at enrollment.

5. Pulmonary status: All children will be co-enrolled in 97-CH-0064, and will have pulmonary function testing through that protocol. Tests will be scheduled as required for that protocol; namely, PFTs every 2 years if normal, every year if abnormal.

OFF STUDY CRITERIA

1. Patients who develop scoliosis greater than 40° and/or patients who progress to severe basilar invagination during the study will be removed from the study.

Failure to comply with the outlined procedures (blood draws, endocrine testing, bone biopsies, and visit schedule) is also a criterion for withdrawal from the protocol.

2. Patients who become pregnant.

NATURE OF PROCEDURES

6 or 12 hour growth hormone evaluation: A heparin lock will be inserted prior to the overnight unstimulated growth hormone evaluation. Blood samples will be collected for growth hormone every 20 minutes for 6 or 12 hours. [17] We anticipate that the majority of patients will weigh enough for either the 6 or 12 hour test.

Somatomedin generation test: Patients will be given a daily subcutaneous injection of synthetic growth hormone, 0.033 mg/kg, for 5 days. [14] Blood will be drawn as described in the protocol section of this document.

Tetracycline-labeled iliac crest biopsy: To assess dynamic parameters of bone formation, tetracycline, which has high affinity for hydroxyapatite in its early states of organization), will be administered orally at a dose of 15-20 mg/kg/d (max 900 mg/d) for two 2-day courses separated by a 10-day free period. This generates two distinct fluorescent lines along the actively forming bone surfaces and allows exact assessment of the bone formation and mineral apposition rates. Bone cores will be taken from alternate iliac crests using a 5 mm Bordier trephine. Careful procedure will allow collection of specimens in which the architecture of trabecular and cortical bone is maintained. Dynamic and static histomorphometric parameters of bone formation and resorption will be measured according to the guidelines of the ASBMR Histomorphometric Nomenclature Committee. [19]

Growth Hormone Injections: Humatrope® is the synthetic human growth hormone manufactured by Eli Lilly and Company. It is identical in amino sequence to the natural human hormone. There is now considerable experience with this drug. Parents will be informed of the potential risks of insulin-resistant hyperglycemia, decreased serum thyroxine, slipped capital femoral epiphysis and allergic reactions. A comprehensive, detailed list of all potential risks is included in the informed consent form. All patients will be given the dose 0.06 mg/kg/day for six days/week.

HAZARDS AND DISCOMFORTS

Endocrine evaluation for Parts A and B: Participants in this study will have a heparin lock inserted prior to the overnight serial growth hormone sampling. This heparin lock will be used to withdraw blood samples for the pulsatile growth hormone study.

Our experience with the somatomedin generation test has been more positive with separate venipunctures for each sample; we are not planning heparin lock insertion for this stimulation test. During the somatomedin generation test the patient will have the discomfort of daily subcutaneous injections. No additional side effects are expected from this short-term administration of synthetic growth hormone.

The maximum blood volume required for the endocrine evaluation when all testing is done in one visit is 76 cc, which can safely be obtained from a 15.2 kg child. We expect to do this testing in 2 separate visits, 6 months apart so as not to exceed the safe blood limit parameters defined by Clinical Center policy. NIH policy limits the volume of blood drawn from children to 9.5 milliliters per kilogram of body weight in any 8-week period of time and 5 milliliters per kilogram of body weight at any one time.

Iliac Crest Bone Biopsy: Bone biopsies are now performed in the operating room at the NIH with patients under general anesthesia. Anesthesiologists from the Department of Anesthesia and Surgical Services at the NIH clinical center manage general anesthesia and closely monitor risks associated with general anesthesia such as suppression of respiratory and cardiac function. With appropriate sedation, an iliac crest biopsy is a relatively simple procedure. Plugging of the biopsy site with Surgicel or gel foam, together with placement of a compressive dressing, prevents bleeding and also encourages rapid clot organization. Two small stitches will be used to close the skin wound. In our experience, the short course of tetracycline administration has never provoked tooth staining. The drug should be administered after meals and long duration exposure to sunlight prevented during those days. Rarely, the drug causes skin hypersensitivity to sunlight that may induce first degree sunburn. Discomfort in the hours following the biopsy is easily controlled with pain relievers such as Tylenol or Tylenol with codeine.

Humatrope® injections: Parents will be taught to administer subcutaneous injections of Humatrope®. They will use an insulin syringe and needle for this daily procedure. There is no discomfort connected with the delivery of the hormone itself. The discomfort will consist of the insertion of a very small needle under the skin and should be minimal.

ADVERSE EVENTS

All serious, unexpected adverse events (those not included in the investigators brochure), related to the use of Humatrope® will be reported to Eli Lilly and Company. Unexpected, serious adverse events will be reported to the FDA as well, within 15 days of the event, and within 7 days in the case of a death or life-threatening event. The known risks of

growth hormone administration are listed in attachment I. These are expected risks and therefore will not be considered reportable to the FDA.

Adverse events that will be reported to the NICHD IRB will include those events reportable to the FDA and Eli Lilly. In addition, we will report the following adverse events related to the bone biopsy procedure:

1. Prolonged bleeding at the biopsy site, which we define as bleeding lasting longer than 24 hours post biopsy
2. Post biopsy infection at the biopsy site; defined as an infection diagnosed and treated by the private physician at home within 7 days of the biopsy.

Frequent fractures are a cardinal feature of patients with OI. Fractures may not be consistently documented by x-ray or history, and can occur in clusters. For these reasons, fracture incidence is not an accurate measure of progression or worsening of osteogenesis imperfecta. Fractures are not defined as reportable adverse events.

RADIATION EXPOSURE

The effective dose calculation for the radiographic studies involved in this protocol is 0.43 rem. The amount of radiation in this study is within the dose guideline (0.5 rem) established by the NIH Radiation Safety Committee for pediatric research subjects, and is deemed a slight increment above minimal risk. The amount of radiation that patients will receive in this protocol is equivalent to the amount of radiation exposure from natural background sources in about a year and a half. The highest individual organ exposures will be to the skin, muscle, and bone surfaces (4 rem each). The radiographic studies described in this study are acceptable to obtain the desired research information, and present the prospect of direct benefit to the individual subjects. The radiographic procedures will be performed by or under the supervision of a radiologist in the NIH CC Radiology Department.

We invite the parents of our patients to bring recent films taken at home which can be copied at the Clinical Center and returned to them, thus eliminating the need for repeat films. All parents will be informed that this is a possibility, and told to request that a ruler be placed on the long bone films.

The most obvious potential benefit that participants in this study might expect is improved linear growth rate, leading to, over time, an improved final adult stature. At this time, we cannot predict who will and will not respond, so this benefit is a potential for all participants. For those children who respond to the growth hormone, our earlier data showed an improved quality of bone after 1 year of growth hormone treatment, as well as improved bone density. [9] By adolescence and adulthood, many people affected with OI begin to develop cardiac and pulmonary abnormalities that may be secondary to a small thoracic cage. By increasing linear length, to include trunk height, we expect a final potential benefit to be prevention of possible cardiac and pulmonary deficiencies.

Informed consent will be obtained from a parent or legal guardian of all children participating in this study, by the principal investigator or an associate investigator. For children who are 7- 8 years old, an assent will be obtained by the principal investigator or an associate investigator. Children under the age of 7 years will be given age appropriate teaching for each procedure they will be having.

DATA and SAFETY MONITORING PLAN

Study Staff Responsibilities

The Principal Investigator, Joan Marini, is responsible for all aspects of the study.

Source Documentation

Joan Marini, MD, PhD, is responsible for coordinating data collection and will review the data for accuracy and completeness within 2 months of each subject visit, including review of patient consent documents. An evaluation of patient recruitment, accrual, and retention as specified in the protocol will be ongoing. Review of literature and results of related studies will be assessed throughout the study for any impact on patient safety or ethical questions.

IRB and DSMC Documentation

All IRB documentation can be found in PTMS. The Principal Investigator, Joan Marini, is responsible for maintaining IRB documentation, including records of all reviews of the study and submissions to the IRB. This protocol does not meet the criteria as outlined in the NIH HRPP SOP 17 for data to be submitted to a data safety monitoring committee. Clinical Trial Studies (non IND/IDE) will have random audits performed by the NICHD Office of the Clinical Director (policy: <https://science.nichd.nih.gov/confluence/display/ocd/Protocol+Navigation>).

Consent:

“For subjects who were minors at the time of consent and are now age 18 years or older, the PI has requested a waiver of consent (45 CFR.46.117) for continued analysis of their data. The research involves no more than minimal risk and a waiver will not adversely affect the rights and welfare of the subjects. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from breach of confidentiality. Continued research could not be carried out without the waiver as several protocol participants signed their assent more than 10 years ago and the PI has lost touch with about 3/4 of the patients. Wherever appropriate, subjects will be provided with additional pertinent information regarding any findings learned from the analysis of their data”.

Adverse Event Procedures and Documentation

All Unanticipated Problems (UP), Unanticipated Adverse Device Effects (UADE), Protocol Deviations (PD), deaths, and Adverse Events (AE) will be reported to the IRB or the Clinical Director (CD) using PTMS, in accordance with SOP 16. When PTMS is not available, the NIH Problem Report Form will be used.

(https://federation.nih.gov/ohsr/nih/ohrdocs/NIH_Problem_Report_Form_Fillable_DDIR_v1_6-11-13_508.pdf).

All serious UP's and Serious PD's, and will be reported to the IRB and CD as soon as possible but not more than 7 days after the PI first learns of the event. Non-serious UP's will be reported to the IRB and CD, and non-serious PD's to the IRB not more than 14 days after the PI first learns of the event. Deaths will be reported to the Clinical Director within 7 days after the PI first learns of the event. An aggregated summary of all UP's, PD's, and AE's will be reported to the IRB at the time of Continuing Review (CR).

Study Completion

Principal Investigator will maintain subjects' records for at least three years after completion of the study.

EVALUATION OF RESULTS

The primary outcome is the change in growth rate from untreated to treated status. For the first year, a 50% increase in growth rate is considered a positive response. We suppose that growth rate is approximately normally distributed. From random chance, we estimate that the probability of observing a 50% increase in growth without intervention is less than 0.2. Therefore, we would like to test the null hypothesis that the proportion of responders in the population is less than or equal to 0.2 against the alternative that the proportion exceeds 0.2. Using a normal approximation to the binomial and assuming the true action of GH is to result in a population with mean 50% more than the untreated mean, we have 91% power with the sample size of 20.

Other protocol parameters will be correlated with linear growth responders versus non-responders, as well as being analyzed for the group as a whole. These correlations will be made for both 6 month and one-year treatment intervals throughout the study.

NATURE OF FINANCIAL COMPENSATION

No financial payments will be offered to patients or their families.

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