ACTH for Frequently Relapsing and Steroid Dependent Nephrotic Syndrome

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Abstract

ACTH, given in the form of a long-acting, repository injection, has recently been shown to be effective in inducing disease remission in adult patients with nephrotic syndrome. Side effects are decreased compared to corticosteroids and other immunosuppressive agents, making it an attractive therapeutic choice for patients with frequently relapsing and steroid dependent nephrotic syndrome (FRNS and SDNS). No published data exist on the use of long-acting ACTH gel in the pediatric nephrotic population. We propose a multi-center, prospective, controlled open label, randomized trial to evaluate the effects of ACTH on the symptoms and biochemical profile in children with FRNS and SDNS.

Introduction

Treatment of frequently relapsing and steroid dependent nephrotic syndrome (FRNS and SRNS) in children remains challenging. Current treatment exposes patients to morbidity from prolonged, high-dose corticosteroids as well as various immunosuppressive agents that have a variety of serious side effects, including nephrotoxicity[1]. Chronic corticosteroid exposure leads to growth retardation, obesity, decreased bone density, and other complications. Short-term use of corticosteroids is associated with behavioral changes. Furthermore, relapses of nephrotic syndrome are associated with potential complications such as infection and thromboembolic disease[2,3].

During the 1950s, parenteral adrenocorticotropic hormone (ACTH) was an effective treatment for nephrotic syndrome. ACTH was utilized in frequent, often four times daily, high dose injections for days to weeks, necessitating hospitalization for treatment and monitoring[4-7]. Oral prednisone ultimately replaced ACTH.

In recent years, there is renewed interest in ACTH for the treatment of nephrotic syndrome, stemming from adult studies demonstrating its ability to induce remission and improve serum lipid profile in cases where other immunosuppressive regimens have failed[8-10]. In the United States, ACTH is now administered in the form of ACTH gel (HP Acthar Gel®, Questcor Pharmaceuticals, NY, USA), a long-acting, repository injection isolated from porcine pituitary extracts containing $ACTH_{1-39}$, as well as other pro-opiomelanocortin (POMC) peptides. The most common adult dosing regimen is 80 units twice weekly[11]. A randomized pilot trial by Ponticelli et al showed that treatment with twice weekly ACTH for 1 year is comparable to 6 months treatment with methylprednisolone and chlorambucil or cyclophosphamide in achieving and sustaining remission, with mild and reversible side effects in the ACTH treatment arm[12]. It has recently been proposed that ACTH produces antiproteinuric, lipid-lowering, and renoprotective effects via the melanocortin system, in addition to its effect on increasing endogenous steroidogenesis[11].

With its side effect profile, ACTH would be an attractive therapeutic alternative for the treatment of FRNS and SDNS in children, who are especially vulnerable to the long-term adverse effects of corticosteroids and immunosuppressive agents on growth, bone health, and weight gain. To our knowledge, there has not been any published experience with long-acting

ACTH gel for children with nephrotic syndrome. We propose a study to evaluate the efficacy of ACTH on the symptoms and biochemical profile in children with FRNS and SDNS.

Definitions

FRNS	≥2 relapses within 6 months after initial therapy or ≥4 relapses in any 12-month period.
NS	Edema, Up/c >2,000mg/g, or ≥300mg/dl or 3+ protein on Albustix, hypoalbuminemia ≤2.5 mg/l
Relapse	After remission, an increase in the first morning Up/c ≥2 or Albustix reading of ≥2 for 3 of 5 consecutive days.
Remission	Up/c <0.2 or Albustix negative or trace for 3 days.
SDNS	Relapse during taper or within 2 weeks of discontinuation of steroid therapy.
SRNS	Inability to induce a remission with 4 weeks of daily steroid therapy.
SSNS	Attains remission within 4 weeks of daily steroid therapy.
GFR	Calculated by the new Schwartz formula:

$$(0.413 \times height) \div serum\ creatinine$$

Height in cm, serum creatinine in mg/dL

Hypotheses and End-points

Our **hypotheses** are the following:

Hypothesis 1: ACTH gel is superior to no treatment in maintaining remission in children with frequently relapsing or steroid dependent nephrotic syndrome.

Hypothesis 2: Relapses in children with frequently relapsing or steroid dependent nephrotic syndrome receiving ACTH gel will increase when the dose of ACTH gel is reduced by 50%.

Hypothesis 3: ACTH gel will increase the percentage of children with frequently relapsing or steroid dependent nephrotic syndrome that remain relapse free off medication.

Primary end-points:

The primary end-point related to Hypothesis 1 is the proportion of patients in each arm with a relapse during the initial 6 months of treatment.

The primary end-point related to Hypothesis 2 is the proportion of relapse-free patients during the first 6 months and second 6 months of treatment with ACTH. This will include patients initially randomized to ACTH and patients who receive ACTH as rescue therapy following their initial relapse in patients randomized to no treatment.

The primary end-point related to Hypothesis 3 is the proportion of patients who have relapses in the 6 months following completion of one year of ACTH. This will be compared to the

proportion of patients with relapses during the initial 6 months in the patients randomized to no treatment.

Secondary end-points:

Our secondary end-points are the following:

1. The total prednisone exposure over the initial 12 months in the two groups.
2. The number of relapses over the initial 6 months in the two groups.
3. The change in BMI, height SDS, and cholesterol over the study period for both groups

Study Design and Methods

The experimental design is a multi-center, prospective, controlled open label, randomized trial comparing ACTH gel and no treatment in preventing relapses in pediatric patients with frequently relapsing or steroid dependent nephrotic syndrome.

Patients will be randomized in a 1:1 ratio to either no treatment or treatment with ACTH gel. The primary outcome will be the presence of a relapse within 6 months of starting ACTH gel or no treatment.

After initial recruitment, enrollment will begin with a screening visit to determine eligibility and obtain informed consent and assent. Randomization and weaning of all other medications for the treatment of NS will begin after remission has been achieved for those with active relapse. There will be a 2 week overlap of ACTH and current immunosuppressive medications:

1. ACTH will be initiated 2 weeks prior to the completion of the prednisone taper for patients who are receiving prednisone at the time of consent.
2. ACTH will be initiated 2 weeks prior to stopping preventive medications such as tacrolimus, cyclosporin, and mycophenolate.

Patients randomized to no treatment will be followed for up to 6 months or until disease relapse, whichever occurs first. Patients who relapse within 6 months will be given the option of reassignment to the ACTH treatment group after remission has been achieved using conventional corticosteroid therapy.

Patients randomized to ACTH treatment will be given ACTH for 12 months. During the second 6 months, the ACTH dose will be reduced to 50% of the starting dose. The outcome of interest is the presence of relapses after dose reduction. Follow-up will occur throughout the 12 months of therapy, and also for 6 months following the completion of ACTH therapy. The outcome of interest is the percentage of patients with relapses in the 6 months after completing a 12 month course of ACTH treatment.

Visits

Screening visit: The study will be explained to the patient and family. Inclusion and exclusion criteria will be reviewed to determine eligibility. Consent and assent will be obtained as appropriate. Medical history will be recorded. A physical exam will be performed. If indicated, a

plan for prednisone tapering will be explained to the family. The date of the baseline visit will either be determined at that visit or via telephone for patients who are currently in relapse.

Baseline visit: The patient will be seen and have baseline labs (renal function panel, cholesterol, urinalysis, urine protein/creatinine ratio). A urine pregnancy test will be performed in females of childbearing age (achieved menarche) who are randomized to ACTH treatment along with counseling in required birth control. An interval medical history and quality of life (QOL) survey will be performed. Patients will have a physical examination. Patients will be randomized to either ACTH gel or no treatment. Patients will be given Albustix and instructions for daily monitoring of the urine and recording the results. Patients randomized to ACTH gel will receive their first injection in clinic and be taught how to perform injections at home. A stop date for other immunosuppressive medications will be provided, if appropriate, 2 weeks after starting ACTH.

ACTH TreatmentACTH will be dosed by body surface area (BSA), with an initial dose of 80U per $1.73m^2$. After 6 months of treatment, the initial dose will be reduced by 50% (1^{st} reduction), to complete the second 6 months of ACTH therapy.

If patients develop significant side effects on the initial dose, they will have an early dose reduction by 50% at the discretion of each individual site PI (1^{st} reduction). They will complete a total 6 months of treatment with the initial and reduced dose. After 6 months, ACTH will be reduced again by 50% (2^{nd} reduction), to complete the second 6 months of ACTH therapy.

Patients who do not tolerate ACTH therapy despite an early dose reduction will exit the study with reporting of adverse events as appropriate.

Patients who relapse on a reduced dose of ACTH during the second 6 months of treatment will have their dose reverted to the previous dose and complete a total of 12 months of treatment with no further dose reductions.

Patients with two relapses on the highest tolerated ACTH dose will exit the study.

BSA	Initial Dose	1st Reduction (50%)	2nd Reduction (25%)
0.50-0.60	24U = 0.3mL	12U = 0.15mL	8U = 0.1mL
0.61-0.75	32U = 0.4mL	16U = 0.2mL	8U = 0.1mL
0.76-0.95	40U = 0.5mL	20U = 2.5mL	12U = 0.15mL
0.96-1.09	48U = 0.6mL	24U = 0.3mL	12U = 0.15mL
1.10-1.25	56U = 0.7mL	28U = 0.35mL	16U = 0.2mL
1.26-1.45	64U = 0.8mL	32U = 0.4mL	16U = 0.2mL
1.46-1.60	72U = 0.9mL	36U = 0.45mL	20U = 0.25mL
≥ 1.61	80U = 1.0mL	40U = 0.5mL	20U = 0.25mL

*Note: there is rounding of the doses to the closest administrable amount by subcutaneous injection.

Interval Visits

Telephone contact will occur weekly for the first 3 weeks after randomization. This will include screening for adverse events, reviewing medications and timing of medication changes, review of Albustix testing, and reviewing dosing of ACTH if applicable. Patients randomized to ACTH treatment will have two additional telephone contacts one month after ACTH dose reduction or discontinuation. This is to screen for symptoms of adrenal insufficiency.

Follow-up visits in patients randomized to ACTH will occur 1 month, 2 months, 4 months, 6 months, 8 months, 10 months, 12 months, 15 months and 18 months after the baseline visit. An interval medical history (including screening for adverse events) will be performed. Patients will have a physical examination. A renal function panel, cholesterol, urinalysis, urine protein/creatinine ratio, and QOL survey will be obtained at months 6 and 12. Urine pregnancy test, if applicable, will be obtained at months 4 and 8.

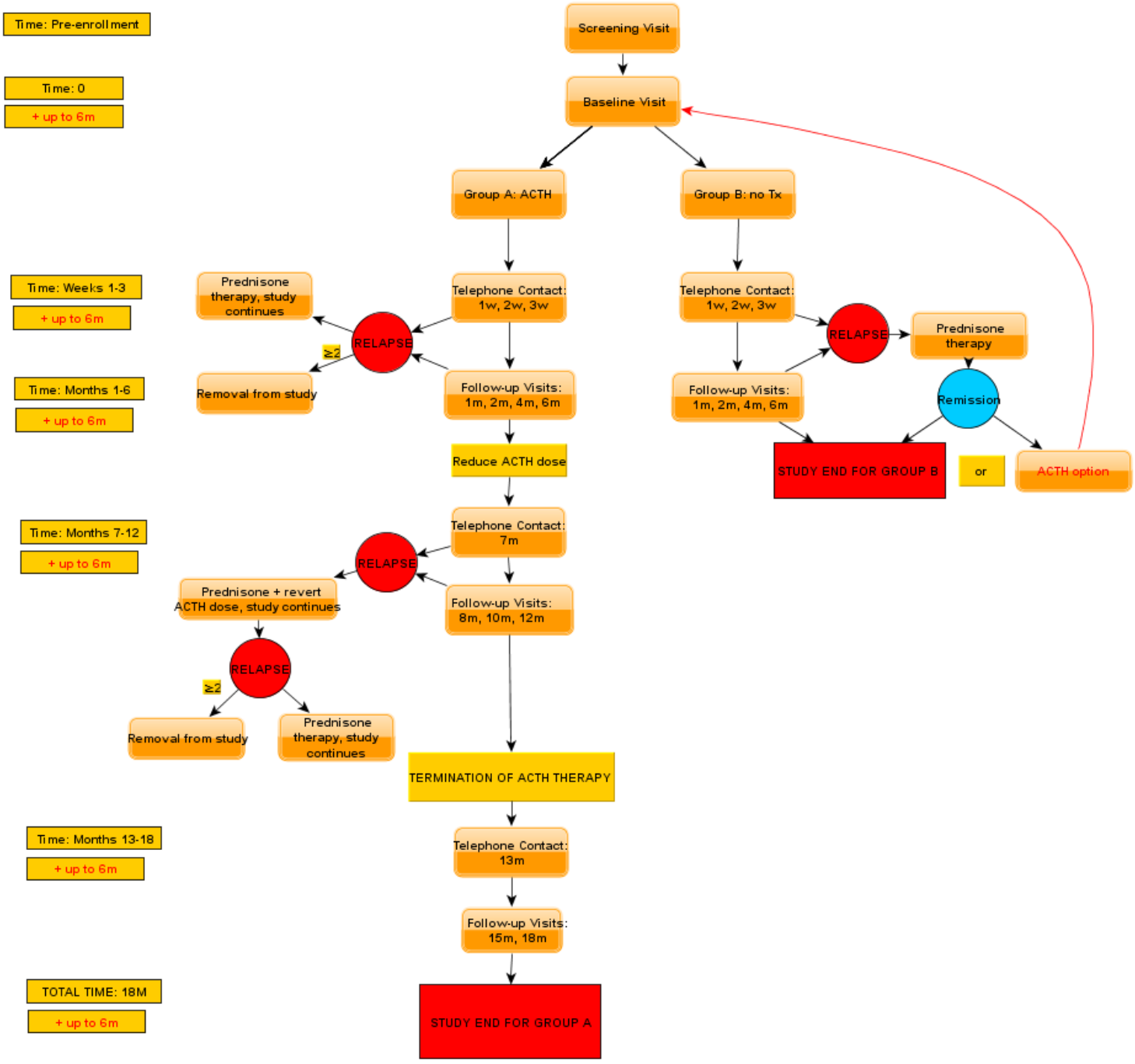
The dose of ACTH will be reduced by 50% after 6 months of treatment Patients who have significant side effects attributed to ACTH will have an earlier dose reduction (i.e., before 6 months) at the discretion of each individual site PI. The PI will be asked to review possible side effects with the patient at each visit and decide if a dose reduction is warranted. A telephone contact will be made 1 month after dose reduction to screen for symptoms of adrenal insufficiency.

Relapses will be treated with prednisone, at 2mg/kg/day or 60mg/m^2/day (maximum dose 60 mg) until remission is achieved, with a subsequent taper off therapy over 4 weeks. For patients receiving a reduced dose of ACTH, the dose will be reverted back to the last effective dosage on which remission was sustained, and continue at that dose until the end of the study. If >1 relapse occurs on the initial ACTH dose, ACTH therapy will be considered a failure and terminated.

The total ACTH therapy duration will be 12 months, after which, the subjects will be seen at follow-up at 15 and 18 months.

Patients who are randomized to no treatment will have follow-up visits up to the time of relapse, at 1 month, 2 months, 4 months, and 6 months. An interval medical history (including screening for adverse events) will be performed. Patients will have a physical examination. A renal function panel, cholesterol, urinalysis, and urine protein/creatinine ratio, and QOL survey will be obtained at month 6. They will be treated with prednisone for any relapses and have the option to be placed on ACTH during the last 2 weeks of the prednisone taper if the relapse occurred within 6 months of the baseline visit. The subsequent visit schedule and procedures will be identical to the schedule for subjects initially randomized to ACTH (i.e., it will include a baseline visit, telephone contacts, and 18 months of follow-up). Alternatively, the patient may elect to be treated via standard of care in collaboration with the treating nephrologist, and the patient will then exit the study.

Flow Chart of Study Course



Participant Selection

Sixty subjects will be recruited from 10-12 large pediatric centers. Subjects may also be identified via physician or self-referral from advertisements placed on NephCure. Additionally, subjects may be recruited from registries of individuals interested in research participation.

Patients and their caregivers will be approached during a relapse of nephrotic syndrome or within 4 months of a relapse. The following criteria will be reviewed during the screening visit to determine eligibility:

Inclusion criteria

1. Age >1 year at onset of nephrotic syndrome
2. Age 2-20 years at time of randomization
3. Estimated GFR > 50 ml/min/1.73 m^2 at most recent measure prior to randomization (Schwartz formula)
4. Steroid responsive nephrotic syndrome throughout clinical course (never required a second agent to attain remission of a relapse of nephrotic syndrome)
5. History of frequently relapsing or steroid dependent nephrotic syndrome (defined as 2 or more relapses within 6 months after initial therapy or 4 or more relapses in any 12 month period OR relapse during taper or within 2 weeks of discontinuing prednisone).
6. Patient is currently in relapse of nephrotic syndrome or had a relapse within the last 4 months (defined as an increase in the first morning urine protein to creatinine ratio ≥2 or Albustix reading of ≥2 for 3 or 5 consecutive days).

Exclusion criteria

1. Prior treatment with ACTH.
2. Cyclophosphamide or rituximab within the last 4 months.
3. Lactation, pregnancy, or refusal of birth control (abstinence qualifies) in females with child-bearing potential.
4. Planned treatment with live or live-attenuated vaccines once enrolled in the study.
5. Participation in another therapeutic trial concurrently or 30 days prior to randomization.
6. Active/serious infection (including, but not limited to Hepatitis B or C, HIV).
7. Malignancy concurrently or within the last 2 years.
8. Systolic or diastolic blood pressure >95% for age/height while receiving maximal doses of 3 or more medications.
9. Prior diagnosis of diabetes mellitus (Type I or II) or fasting glucose >200mg/dL
10. Organ transplantation
11. Contraindications to Acthar: scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, or adrenal cortical hyperfunction
12. Secondary cause of nephrotic syndrome (e.g., SLE)
13. Biopsy demonstrating a diagnosis other than minimal change, FSGS or a variant (mesangial proliferation, IgM nephropathy)
14. Inability to consent/assent

Statistical Analysis

The primary end-point of the study and on which the statistical power is based is the proportion of patients who have a relapse in the 6 months following randomization to either ACTH or no ACTH.

We hypothesize that the 6 month relapse rate for patients receiving no treatment is 70%. In order to detect a 6 month relapse rate of 30% for patients receiving the ACTH gel, we will randomize 30 patients in each arm using a two sided z test with alpha=.05. Our statistical power to detect such a difference is 91% which assumes two interim analyses at 50% and 100% of accumulated information. That is, once 30 patients have 6 month relapse data, we will conduct the first interim analysis. The last one will be completed once we have relapse data on all 60 patients. The table below gives the operating characteristics for such a design:

Number of Patients with 6 Months Data	Boundary p-value
30	0.006
60	0.045

Using the method of Lan-DeMets, we list the boundary p-value for this sequential design. Thus, after our first interim look, we will reject the null hypothesis of equal 6 month relapse rates between ACTH gel and no treatment if our test statistic renders a p-value < .006. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure. The odds ratio of ACTH versus no ACTH, plus the Wald 95% confidence interval, will be also be calculated.

The primary end-point related to specific aim 2 is the proportion of relapse-free patients during the first 6 months and second 6 months of treatment with ACTH. This will include patients initially randomized to ACTH and patients who receive ACTH as rescue therapy following their initial relapse. We will estimate 6 month and 12 month relapse-free rate using the method of Kaplan-Meier and compare treatments using a log-rank test.

The primary end-point related to specific aim 3 is the proportion of patients who have relapses in the 6 months following completion of one year of ACTH. This will be compared to the proportion of patients with relapses during the initial 6 months in the patients randomized to no treatment using a z test statistic. Odds ratios of ACTH vs no ACTH will also be calculated.

We will also compare patients as randomized by secondary endpoints such as total prednisone exposure in 12 months, number of relapses, cholesterol and change in BMI with two sample t-tests. If normality assumptions do not hold, appropriate non-parametric methods will be used.

Growth data collected during the study will be summarized descriptively for each treatment group at each time point. Based on height data collected during the study and published reference height information, the height standard deviation score (SDS, also called z-score) will be computed for each patient at each time point as:

(Height - mean height for that age category) / SD of height for that age category.

Descriptive statistics of this endpoint will be presented by time point and the z-scores will allow identification of potential outliers.

Treatment Assignment and Randomization

Treatment assignments will be stratified according to clinical center. The treatment assignments will be generated by the Data Coordinating Center (DCC) with the use of a pseudo-random-number generator with randomly permutated blocks that will be used to ensure balance between the number of subjects assigned to each treatment (ACTH or no ACTH). Before the study starts, the institutional research coordinator at each clinical center will be given a batch of

20 sealed, sequenced, opaque envelopes containing the treatment assignment and will have a unique ID consisting of the clinical center stratum.

Patients will be assigned to one of the two treatment arms in a ratio of 1:1.

Data Collection and Management

Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

Data collection

Data collection and analysis will be facilitated by the Data Coordination Center (DCC), which will be led by Traci Leong, PhD. They will interact with the PIs, local site investigators, and study coordinators to collect data, analyze the results, and provide reports to the DSMB in a timely manner.

REDCap will be used for data collection and management. The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Using the REDCap Electronic Data Capture (EDC), the designated investigational staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software.

Site staff will not be given access to the EDC system until they have been trained. Validation programs will check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff. The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. There will be regular reports of enrollment by site.

Database Management and Quality Control

The Data Coordinating Center (DCC) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via email. The Principal Investigator and site investigator will be copied on all correspondences. Designated investigator site staff members are required to respond promptly to queries and to make any necessary changes to the data.

After these actions have been completed and the data have been verified to be complete and accurate, the database will be declared locked and made available for data analysis.

Adverse Event Reporting

Screening for adverse events will begin at each telephone contact via interview and screening questionnaire. Formal evaluations of side effects from ACTH will be made at each monthly visit with direct interview, physical examination, questionnaire, and laboratory evaluation. Subjects will be provided with home urinary dipsticks to monitor relapse of nephrotic syndrome. All Serious Adverse Events will be reviewed within the applicable guidelines and submitted to the sponsor and appropriate IRB. Acute exacerbations of the subject's condition that is not in keeping with the natural history will also be reported.

A serious adverse event is defined as: death; life-threatening event; requires or prolongs hospitalization; results in disability significant, persistent, or permanent; pregnancy with a resultant birth defect; causes cancer; or overdoses of a study medication.

In addition to the completion of the appropriate forms, any serious adverse event or serious and unexpected suspected adverse reaction occurring during the study or in a post-study period of one month will be reported to the principal investigator, the Data Monitoring Committee (DMC), the local IRB, the sponsor, the study supporter, and participating sites within 2 business days. The IND sponsor will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

Adverse events that do not meet criteria for Serious Adverse Event will be reported using the Adverse Event Form during the follow up visit. Information regarding the diagnosis, date of occurrence, severity of the event, and therapy will be recorded. A determination of the relationship of the adverse event to the study participation will be made by the Participating Site investigator. Should a relationship be found, results will be reported to the sponsor, the study-supporter, and the DMC within 1 business week.

Data and Safety Monitoring Plan

An external Data Monitoring Committee (DMC) will be constituted prior to the randomization of the first patient. The DMC will consist of a minimum of three individuals outside the Division of Pediatric Nephrology. The individuals shall be practicing clinicians with experience in clinical research. At least one member will be a nephrologist, and two members will be pediatric subspecialists. Details on the membership, responsibilities and working procedures of the DMC will be described in the DMC Charter.

The DMC will perform the first safety review using a data cutoff 6 months after randomization of the first patient and every 6 months thereafter, unless otherwise requested by the Chairman of the DMC. The DMC will also receive reports on a regular basis on all SAEs reported for this trial. One interim analysis and one final analysis are planned. These analyses will coincide with the timing of the scheduled DMC meetings. Recruitment will not be interrupted unless otherwise requested by the Chairman of the DMC. Results of the DMC review will be shared with the PI and all participating sites within 1 business week.

The study would be stopped if the DMC and the PI believe that there is a significant safety issue or that the interim analysis indicates that completing the study is not appropriate. Should a

decision be made to stop the study, a report will be made to all participating sites within 2 business days.

Data Quality and Compliance Site Monitoring

A separate data safety monitoring plan (DSMP) provides details on data quality and site monitoring.

Pharmaceutical Information

See attached ACTH gel (HP Acthar Gel, Questcor Pharmaceuticals, NY, USA) Package Insert.

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