IKANEAT: A RANDOMIZED-CONTROLLED, MULTICENTER TRIAL OF MEGESTROL FOR CHRONIC ORAL FOOD REFUSAL IN CHILDREN 9 MONTHS TO 9 YEARS 0 MONTHS OF AGE

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Study Product: *Megestrol acetate*

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List of Abbreviations

Abbreviation	Description
AE	adverse event
BID	bis in die (twice daily; every 12 hours)
CRF	Case Report Form (either paper or electronic)
DSMC	Data Safety Monitoring Committee
EC	Ethics Committee
eg	for example
EOT	end-of-treatment
etc	et cetera; and so forth
EU	European Union
FDA	Food and Drug Administration
G	Gastrostomy
G-J	Gastrojejunal
g	gram
GCP	Good Clinical Practice
GCRC	General Clinical Research Center
GMP	Good Manufacturing Practice
REDCap	Research Electronic Data Capture

Study Summary

Title	*iKanEat: A, randomized-controlled, multicenter trial of megestrol for chronic oral food refusal children 9 months to 9 years 0 months of age*
Short Title	*iKanEat: Megestrol for Chronic Oral Food Refusal*
Protocol Number	*STUDY00142352*
Methodology	*Multicenter, randomized clinical trial*
Study Duration	*Six years*
Study Center(s)	*Multi-center; 10 sites total*
Number of Subjects	*60*
Diagnosis and Main Inclusion Criteria	*History of chronic oral food refusal and be primarily fed through a G or G-J tube*
Study Product, Dose, Route, Regimen	Megestrol will be dosed at 6 mg/kg/d at weeks 10-11, at 4 mg/kg/d at week 12, at 2 mg/kg/d at week 13, and fully tapered at the end of week 13.
Duration of administration	*4 weeks of Megestrol, 24 weeks of iKanEat behavioral intervention*
Reference therapy	*Placebo for Megestrol*
Statistical Methodology	*The outcome measure for Aim 1 is a binary variable indicating whether a child obtains 90% or more caloric intake on oral feeding at the end of the intervention. A chi-square test or Fisher's exact test will be used to compare the rates of oral feeding between the two groups.*

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

Feeding problems requiring medical intervention occur in 3-10% of children (1). Premature infants are overrepresented among children with feeding problems (2). Improved preterm infant survival has increased the prevalence of feeding problems in older infants and toddlers (3). In addition, severe feeding problems occur in 40-70% of children with chronic medical conditions (4,5). Neonates with long intensive care hospitalizations may lose opportunities for learning to eat and may associate eating with pain or discomfort (6). Gastrostomy (G-) and gastrojejunal (G-J) tube feeding requirements may persist for months or years resulting in chronic oral food refusal. As the prevalence of gastrostomy tube feeding has increased, so have the challenges associated with managing a child with tube feeding and transitioning a child from tube to oral feeding (7,8). Previous research on transitioning children from tube to oral feeding indicates that most programs are inpatient or intensive day treatment, and many children are not successful (8).

Our team developed a novel interdisciplinary outpatient protocol for transitioning children from tube to oral feeding (9,10) called iKanEat. Data indicate iKanEat is effective for transitioning tube fed children to eating by mouth. iKanEat results in statistically significant and clinically meaningful increases in oral eating. iKanEat is composed of several key components, including two medications – amitriptyline and megestrol. However, our most recent work (HD066629)(11) demonstrated that amitriptyline is not a necessary component of the protocol, as all children who completed the protocol consumed 100% of their calories orally at post treatment regardless of receiving amitriptyline or placebo. The current proposal is a randomized controlled trial of the second medication (megestrol) compared to placebo, to ensure that the addition of a 4-week course of megestrol improves child outcomes within the iKanEat protocol. Because corticosteroids can have significant side effects, it is critical we determine if the benefits of megestrol as part of iKanEat outweigh the risks of the medication.

1.1 Background

Gastrostomy Tube Feeding

Gastrostomy (G-) and gastrojejunal (G-J) feeding tubes are placed in infants and children who refuse to eat or are unable to eat enough to sustain normal growth. Common medical causes of inadequate weight gain include neurological disease, congenital heart defects, chronic pulmonary disease, renal failure, genetic disorders, anatomic abnormalities, behavioral disorders, and oropharyngeal dysphagia (4,19). Although usually intended as temporary, short-term solutions to medical complications, feeding tubes can become a permanent conduit for enteral nutrition.

Although tube feeding routinely saves the lives of children who are unable or unwilling to eat by mouth, chronic tube feeding is a burden to patients, caregivers, and families. First, the decision to have a G-tube placed is difficult for caregivers (20). Once it is placed, caregivers cope with complications including vomiting, diarrhea, infection of the G-tube insertion site, granulation tissue, and leakage of gastric contents (21). Stress levels of caregivers often increase after G-tube placement (22). Because eating is such an integral part of culture, there are many mealtime socialization issues that children and parents miss when the child is tube fed (20). In addition, parents report negative issues secondary to G-tube feeding such as sleep disruption and deprivation, restricted ability to leave the home, childcare problems, negative attitudes of others toward feeding, and difficulties finding a place to feed (21). Although some

studies do find that G-tube placement can improve quality of life for parents in the short term (23), there is consensus that delaying the transition from tube to oral feeding has negative medical, emotional, and economic consequences (21,24).

Transitioning to Oral Feeding

Existing treatment options for transitioning children with severe feeding problems from tube to oral feeding include outpatient, inpatient, and day treatment. The most widely available treatment option for severe feeding problems is outpatient treatment by a multidisciplinary team (25). These teams include professionals from multiple specialties, including pediatric gastroenterology, psychology, speech, occupational therapy, and nutrition (4). Outpatient treatment is typically covered by health insurance, and can be tailored to meet the needs of the patient and family. Typically the patient and family see the providers regularly (i.e., monthly, quarterly) to receive recommendations that are then implemented in the home. Despite the prevalence of outpatient feeding programs, there is little published evidence on outcomes of these programs.

Inpatient programs take place in a hospital setting, and are justified when: 1) a child's feeding problems are leading to severe weight loss; 2) outpatient treatment has proven unsuccessful; and/or 3) parents are willing to participate (increasing the likelihood of generalization to the home setting, (22)) The advantages of inpatient treatment include reduced access to food between meals and the ability of the professionals to feed meals daily (22). These types of inpatient treatment programs are effective at increasing child oral intake and decreasing mealtime behavior problems (23). Yet, there are many drawbacks to inpatient treatment including high cost, large burden on the family, extensive demand on professionals, and difficulties with generalization of treatment gains to the home environment (23).

Day treatment programs have become more common in the last decade. They capitalize upon many of the strengths of an inpatient program mentioned above, but have lower costs (due to the lack of overnight stays). However, cost is still high, and some experts have expressed concern that treatment gains may not generalize to the home environment (24-26).

Therefore, although treatment options do exist for tube fed children, empirically supported inpatient treatment programs are intensive and expensive, and there is little evidence that outpatient programs are effective.

1.2 Investigational Agent

Oral Suspension: Each mL of lemon-lime flavored oral suspension contains: megestrol acetate 40 mg. Inactive ingredients: anhydrous citric acid, natural and artificial lemon-lime flavor, polyethylene glycol 1 450, polysorbate 80, purified water, sodium benzoate, sodium citrate dihydrate, sucrose and xanthan gum. Bottles will be stored at room temperature (15 to 30°C). Protect from temperatures above 30°C (41).

The precise mechanism of action by which megestrol produces its antineoplastic effects is unknown at present. Pharmacologic doses of megestrol exerted a direct cytotoxic effect on human breast cancer cells in vitro and proved capable of modifying and abolishing the stimulatory effects of estrogen on breast cancer cell lines. Megestrol may have other mechanisms of action as well, including an antiandrogen activity, suppression of adrenal androgens, and possibly the inhibition of enzymes, e.g., 5 a-reductase, critical to androgen metabolism within the prostate. The precise mechanism of action by which megestrol produces its antianorexic and anticachectic effects is also unknown at present. The gain in weight associated with megestrol is associated with increased appetite, an increase in fat and body cell mass (41).

1.3 Review of Literature

Feeding

Our team has published several studies of pediatric feeding difficulties. Our early work examined the relationship between feeding difficulties and medical complexity (27), and found that by the time of introduction of solid food, preterm children more often demonstrated difficulty than full-term children. Also, medical factors, primarily the need for breathing assistance, accounted for more of the variance in this relationship than prematurity alone. We have also assessed parent perceptions of mealtime behaviors in children who are tube fed, and learned that parents report surprisingly high levels of stress around the mealtime, both for themselves and their children (28). We have also examined pediatric sensory processing issues related to feeding problems (29) and found that 67% of children who present for treatment have sensory profile scores in the abnormal range. Also, co-occurring diagnoses are frequent in the areas of developmental, gastrointestinal, and neurological areas. This foundational work led to the multidisciplinary protocol which we call iKanEat that was designed to move these complicated children to oral eating on an outpatient basis.

Clinical Data: iKanEat

In 2008, our team published a retrospective chart review of the first 9 patients to undergo our iKanEat tube weaning protocol clinically (30). At that time, the protocol included two medications (amitriptyline and megestrol) as well as behavioral and oral motor/sensory components. Results from this initial retrospective study indicated that the nine initial patients were 100% orally fed at the end of the intervention period, and 8 of the 9 were 100% orally fed six months later (one patient with cerebral palsy had stamina issues and was only able to sustain 50% of intake orally over the long term). This pilot work led us to NIH funding to conduct a randomized controlled trial of amitriptyline, one of the two medications in the protocol (HD066629). The findings (11) suggest that 100% of children who completed the protocol moved from tube feeding to total oral feeding, regardless of group assignment (amitriptyline, placebo). More specifically, of the children who completed the 6 month protocol, % kilocalories/day obtained orally (our primary outcome measure) increased statistically significantly from M = 31.51% (SD = 16.09%) to 100%. Therefore, it does not appear that amitriptyline is a necessary component of the iKanEat protocol.

Parent Stress

During the iKanEat protocol, we expect the child to lose weight during weeks 10-14 as the children taper off the tube. We inform parents of this expected weight loss and monitor the children closely. Despite this, in the previous trial there were instances of parents withdrawing their children during this weight loss period despite the physician guidance that the weight loss was expected and safe. It is critical that we learn more about this stressful period of the iKanEat protocol so we can better help parents through this transition. The current study design will allow us to learn more about how and when parent stress changes throughout the protocol in order to target supplemental treatment efforts related to parent stress.

Quality of Life.

Our most recent study (HD066629) also examined the role of pain and quality of life in tube weaning. Findings demonstrate improvement in pain symptoms ($t = 1.85$, $p = .006$) and in several areas of quality of life (i.e., growth and development, $t = -2.285$, $p < .05$; behavior, $t = -2.376$, $p < .05$; general health perceptions, $t = -2.232$, $p < .05$; parental impact: emotional and time, $t = -3.718$, $p < .005$) in the transition from tube to oral feeding.(11) In the current protocol we will assess whether successful transition to oral feeding has an effect on parent and child quality of life.

Remote Interventions.

Our team has extensive experience delivering multidisciplinary feeding team clinical visits via interactive televideo. These visits are delivered as part of routine feeding team care in our clinic, and include both new patient visits and return patient visits. This clinical experience will serve our team well regarding the current scope of work.

Gut Microbiota

The gut microbiota refers to the species of bacteria living in the gut, and plays an essential role in digestive and immune function. Little is known about the effect formula feeding has on the microbiome, and the effects of transitioning from tube feeds to oral feeding. In the current protocol, we will assess whether successful transition to oral feeding has an effect on the gut microbiota.

Most tube fed children receive a commercial formula through their tube as these formulas are easy to prepare and safe. However, some children do experience gastrointestinal discomfort with tube feeding, and recently, some clinicians and parents have been exploring the use of pureed diets to remedy these issues (e.g. retching, coughing). Very few studies have been conducted examining a blended diet, but Pentuik et al.[47] studied 33 children receiving a pureed diet by tube. Results indicate that both gagging and retching (73% of patients with 50% reduction in symptoms) improved when children were moved from a formula diet to a pureed diet. A more recent study demonstrated increased microbial diversity in 17 tube fed children, transitioned from commercial formula to a blenderized diet.[48]

Research indicates that both diet[49, 50] and the introduction of solid foods have an effect on microbiota.[51] In fact, changes in the gut microbiota can be seen as rapidly as 24 hours after dietary changes occur.[52, 53]

There are no published pediatric studies to date examining the differences in microbiota between children who are tube fed versus fed orally.

Summary

Our previous work suggests that iKanEat is effective in moving children from tube to oral eating, and that amitriptyline does not improve the outcomes associated with the protocol. However, we do not know if the remaining medication (megestrol) improves the outcomes associated with iKanEat. As all medications have risks, it is necessary to test this remaining medication to determine if the risk is outweighed by the benefit the medication brings to the iKanEat protocol.

Rationale

Tube fed children have few treatment options for moving from tube to oral feeding, causing substantial economic impact on their families and the health care system, as well as negatively impacting many parent and child factors including stress and quality of life. Previous research by our team detailed above indicates that iKanEat is an effective weaning protocol when used in combination with megestrol. The current study will provide important information about one of the only empirically supported outpatient treatment protocols for moving children from tube to oral eating, and will also provide much needed information on parent stress and parent and child quality of life during this transition period.

1.4 Dose Rationale and Risk/Benefits

The dose of the megestrol was based upon the preliminary clinical data published.

2 Study Aims

The primary aim of the current study is to conduct a randomized controlled trial of a 4-week course of megestrol, the only remaining medication that is part of the iKanEat protocol, to ensure that the addition of megestrol results in improved child outcomes. The second aim is to assess the safety of megestrol as part of the iKanEat protocol. Our previous work (as well as work by others) suggests that a 6 week course of megestrol can lead to adrenal insufficiency in some children (11-14), so as part of the current protocol, we will assess the safety of a 4 week course of this drug.

Finally, parents of tube fed children encounter multiple psychosocial stressors regarding tube feeding (15) These include concerns about their child's survival due to their underlying medical issues, feelings of "failure" due to their inability to feed their child orally (16), increased feelings of stress around the tube feeding (17) and decreased support from others due to the tube feeding (18,19). Our research indicates that quality of life can be poor in tube fed children (11), even more so than children with cancer or burns. Given the significance of these issues, the third aim of the study is to examine the effect of the transition from tube to oral feeding on parent stress and parent and child quality of life.

Aim 1: To assess the efficacy of megestrol as part of the 24 week iKanEat protocol.
Hypothesis 1: Children randomized to the megestrol group will be significantly more successful in making the transition to oral feeding (defined as obtaining at least 90% of calories orally) than children randomized to the placebo group.

Aim 2: To assess the safety of 4 weeks of megestrol as part of the 24 week iKanEat protocol.
Hypothesis 2A: Children randomized to the megestrol group will not differ from control children in morning cortisol classification level (low, average, high) and will remain within the normal range at all time points. Analyses 2B: Exploratory analysis will determine which, if any, covariates (gender, age, and diagnoses at week 0, diagnoses at birth) are related to abnormal morning cortisol levels.

Aim 3: To examine the effect of the transition from tube to oral feeding on parent stress and parent and child quality of life. Hypothesis 3A: The transition to oral feeding will temporarily increase parent stress at week 14 at the cessation of tube feeding, with a return to baseline by week 24. Hypothesis 3B: The transition to oral feeding will increase parent/child quality of life at 24 weeks compared to week 0. Children with feeding tubes have few options for treatment other than extensive inpatient stays and expensive day treatment programs. iKanEat offers an outpatient, less intensive, empirically supported effective treatment option that can improve the lives of children and families. It is imperative that we determine the efficacy and safety of the protocol including 4 weeks of megestrol before we move toward broad dissemination of the iKanEat protocol.

Aim 4: To examine the effect of the transition from tube to oral feeding on the gut microbiome. Hypothesis 4A: The transition to oral feeding will increase the variety of food consumed orally, thus diversifying the gut microbiome by week 24. Hypothesis 4B: Children who are on a blended diet formula at week 0 will have a more diverse microbiome than children on commercially prepared formula prior to transitioning to oral feeding (Week 0, 10). Little is known about the gut microbiota of children who transition from formula feeding to oral feeding. Determining the changes in the gut microbiome could add to general knowledge about how the gut microbiome adapts to changes in diet over time in children who transition from commercial or blended formulas to a diet consumed orally.

3 Study Design

3.1 General Design

This is a multi-center, randomized, placebo-controlled, double-blind clinical trial. The primary focus of the study is the evaluation of the effectiveness of treatment with megestrol as part of a 24 week behavioral feeding protocol in transitioning from tube to oral feedings in a pediatric population. Approximately 60 pediatric subjects matching the criteria for eligibility will be enrolled in the study and randomized to receive either megestrol (n=30) or placebo (n=30).

3.2 Primary Study Endpoints

Percent Kilocalories Obtained Orally will be the primary study endpoint. This measure will be obtained using the three day 24 hour food recall. The 24hr food recall is a standardized five-pass method, developed by the US Department of Agriculture for use in national dietary surveillance. Although there are weaknesses to every method of dietary assessment, this one was selected as it is widely used in several large trials and data suggest it is the most valid and reliable method of dietary assessment for children (35) The data will be collected using highly standardized probes by trained research staff, and parents will be presented with paper food models and measuring devices prior to interviews to reference during the recall. Recalls will be analyzed with the Nutritional Data System for Research, version 2016; University of Minnesota, Minneapolis, MN. Although a plethora of information is available from this analysis, the current study will focus on total daily oral calorie intake. This measure will be completed the week following Clinic Visits at weeks 0, 10, 14 and 24.

3.3 Secondary Study Endpoints

Parent stress and parent and child quality of life will be the secondary study endpoints and be completed by parents at Clinic Visits at weeks 0, 10, 14, and 24.

1. Parent Stress (The Pediatric Inventory for Parents – PIP36). Parent stress will be measured via the Pediatric Inventory for Parents, a 52 item parent questionnaire developed to measure parent stress around caring for a medically complicated child. The measure has a total and four domain scale scores (communication, medical care, role function, emotional function). For the purposes of the current study, we will use only the total score. The measure has been shown to be a valid and reliable measure of pediatric illness-related parenting stress (36).

2. Child Health-Related Quality of Life (Infant Toddler Quality of Life – ITQOL47). Child quality of life in children <5 years old will be measured with the Infant Toddler Quality of Life short form questionnaire, validated for children 2 months through 5 years of age. The ITQOL has 47 items which result in 9 multi-item scales with well-established reliability (Crohbach's alpha > .70) and validity. Similar to our previous work (11), we will use the multi-item scales in our analyses.

3. Child Health-Related Quality of Life (Child Health Questionnaire Parent Form – CHQ-PF50). Child quality of life in children ≥ 5 years old will be measured with Child Health Questionnaire Parent Form questionnaire. The parent-reported CHQ is normed for ages 5-to-18 and measures 14 unique physical and psychosocial concepts. The CHQ has 50 items and scores for the parent-reported versions can be analyzed at the concept level (CHQ Profile Scores) or combined to derive an overall physical and psychosocial score, (CHQ Summary Scores).

4. Parent Quality of Life (SF-36v2). Parent Quality of Life will be measured with the widely used Parent Quality of Life Short Form 36, version 2. Over 4000 studies have used the SF-36, making it a widely accepted measure, and v2 has improved reliability (α = .73-.90), and validity (38). The 36 questions with 5 point scales have 8 scaled scores: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role

functioning and mental health. As is typical, we will convert individual scores to z scores, resulting in a standardized combined score (39). This standardized combined score will be used in analyses, as well as specific subscales that previous research indicates may be sensitive to the current intervention (Growth and Development, Behavior, General Health Perceptions, Parental Impact: Emotion, Parental Impact: Time).

5. Impact of Pediatric Chronic Health Conditions (PedsQL 2.0, Family Impact Module). The impact of pediatric chronic health conditions on parents and the family will be measured with the PedsQL 2.0, Family Impact Module (63). This 36-item survey measures parent self-reported physical, emotional, social, and cognitive functioning, communication, and worry. In addition, the Module assesses parent-reported family daily activities and family relationships.

6. Patient Health Questionnaire-9 (PHQ-9). The Patient Health Questionnaire (PHQ)-9 is a 9-item measure of depressive symptoms. It is used to provisionally diagnose depression and grade severity of symptoms in general medical and mental health settings. Scores each of the 9 DSM criteria of MDD as “0” (not at all) to “3” (nearly every day), providing a 0-27 severity score. This measure asks about the parent’s thoughts of suicide or self-injury. Study staff will view the responses to this measure within 3 days of the measure being completed. If a parent indicates suicide or self-injury ideation on the measure, the Lead Site PI who is a licensed child psychologist will be notified. The Lead Site PI will then contact the parent to decide if a referral to local support centers is necessary.

7. General Anxiety Disorder-7 (GAD-7). The GAD-7 is a 7-item screening tool and symptom severity measure for the four most common anxiety disorders (Generalized Anxiety Disorder, Panic Disorder, Social Phobia and Post Traumatic Stress Disorder). Higher GAD-7 scores correlate with disability and functional impairment.

8. Impact of Event Scale – Revised (IES-R). The IES-R is a 22-item self-report measure (for DSM-IV) that assesses subjective distress caused by traumatic events. It is a revised version of the older version, the 15-item IES (Horowitz, Wilner, & Alvarez, 1979). The IES-R contains seven additional items related to the hyperarousal symptoms of PTSD, which were not included in the original IES. Items correspond directly to 14 of the 17 DSM-IV symptoms of PTSD. Respondents are asked to identify a specific stressful life event and then indicate how much they were distressed or bothered during the past seven days by each "difficulty" listed.

9. Demographics. Families will complete a demographic questionnaire regarding age, race, ethnicity, income, free/reduced lunch status, and parental education, along with a medical history questionnaire asking about diagnoses at birth and diagnoses at week 0. These variables will be used to describe our sample and in any covariate analyses

10. Gut microbiota. Stool will be collected at each of the 4 clinic visits (Weeks 0, 10, 14 and 24). Once participants are consented, they will be provided with a toilet hat and sterile cup for stool collection. Once collected, stool will be stored in the sterile collection cup in the participant’s freezer, until it is transferred or shipped on ice to a -80° C freezer at the study site. Each sample will be labeled with less than 8 characters and each label which matches the participant ID and will start with a letter (labels may not start with a number; per Novogene guidelines). Micro tubes will be shipped on dry ice to Novogene, where samples will undergo 16s rDNA sequencing utilizing HiSeq PE250. Sequencing will occur in the V4 region with primer 515F and 806R. Data output will be 100,000 raw reads per sample.

11. Clinical care measures. Height, weight, and vital signs will be obtained at clinic visits 1-4. These measures are routine clinical care, but will the data will be used for research purposes.

12. Tube Feeding Parent Report. Some participants may receive tube feedings after the protocol dictates that they should be fully weaned due to an unsuccessful tube feeding wean or an acute illness where the child needs to temporarily resume tube feedings. Caregivers who are giving tube feedings after the weaning phase of the protocol at Week 12 will be asked to self-report the amount of tube feeding their child is receiving. The survey is four questions and asks parents to report the volume of formula given, the approximate % of total calories from tube feedings, and the reason tube feedings were given. The survey will be sent to parents daily while the participant is receiving tube feedings. Once the participant is no longer receiving tube feedings, they will not be asked to complete the survey.

    Post-Intervention Survey and Qualitative Interview. The study team will conduct an online survey and qualitative interviews over the phone with parents of children who have completed the intervention. Parents who choose to participate will be verbally consented over the phone. The survey ask parents will also be asked to self-report their child's current height, weight, and tube feeding status. The 1-hour interview will ask parents about their experience of having a child with feeding issues, opinions regarding the iKanEat intervention, the health coaching, and the tube wean transition. Parents will be paid $20 for completing the online survey, and up to $80 for the phone interview. In total, parents may receive up to $100 via an electronic Amazon gift card. De-identified structured interview audio recordings will be transcribed by a professional transcription service.

13. Other considerations. All children already receiving intensive feeding therapy will be excluded (see Participant section). Participants will continue treatment with their multidisciplinary feeding teams (typically 6-10 weeks between visits at our participating sites) and any other therapies throughout the 24 week intervention protocol. Because these children are medically complicated, often with deficits in many areas, this is important for the welfare of the children. Therapies outside of the iKanEat protocol will be assessed via the post-treatment questionnaire at the final clinic visit (week 24) and be available for use in analyses as covariates if necessary. Also, once the study is completed and all measures are turned in to the study team, participants will be unblinded by the statistical team, informed of their group (megestrol/placebo) and scheduled for follow up care with their multidisciplinary feeding team as appropriate.

3.4 Primary Safety Endpoints

Safety Interviews

To monitor for negative side effects, patients will be interviewed during clinic visits and tele-visits for any negative gastrointestinal, behavioral, feeding, or other negative sequela suspected to result from our treatment. Participants will be asked to measure the child's weight using a digital home weight scale during tele-visits to monitor changes in weight.

Subjects will be considered "at risk" and reviewed by the medical monitor and site PI if either of the following two conditions. The medical monitor and site PI will determine if it is safe for the participant to continue in the study (or, under what conditions it may be safe for the participant to continue) given all patient characteristics, including baseline weight for height ratio or BMI percentile.

1) If more than 0.5 kg of weight is lost consistently per week over three consecutive weeks
2) If the subject experiences 10% loss of total body weight

If any negative outcomes are identified they will be reported to our Data Safety and Monitoring Board and proper steps will be taken.

Laboratory Tests

Children will also have laboratory measurements to assess megestrol safety.

1) Morning Cortisol. The blood for the morning cortisol test will be drawn before 8am by the local laboratory or mobile phlebotomy services to test for adrenal insufficiency. The test will take approximately 1 mL of blood and will be drawn at weeks 10 and 14 for all subjects. Participants taking inhaled or intranasal steroids will take an additional blood draw at week 0. If an abnormal value is measured, a repeat morning cortisol level will be obtained. Every effort should be made to complete a redraw at the earliest convenience, within 7 days. The medical monitor will be on the weekly team calls, so she will be able to advise based on specific circumstances. If the 2nd test is also abnormal, the study protocol will be paused, and a pediatric endocrinologist will be consulted to determine if a formal in-person consultation is needed with endocrinology. The subject may either resume the protocol or be removed from the study pending the endocrinologist and study team's assessment.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Males and females aged 9 months to 9y0m0d at the time of consent.
2. Able to obtain parental or legal guardian written informed consent from subjects as applicable by local laws and regulations.
3. Subjects must have a G or G/J tube.
4. Subjects must receive over 80% of their total daily calorie needs from a tube in order to be classified as tube dependent.
5. Subjects must have a ≥ 3 month history of feeding problems as identified by a diagnosis from a multidisciplinary feeding team, and must have permission from the physician on the team to ensure that they are medically stable enough to participate in a weaning study. *(Please refer to Medically Stable Screening Form to help guide assessment).*
6. Subjects must possess the oral motor skills necessary for eating according to Table 1 in the Appendix.
7. Subjects must possess behavioral skills necessary for mealtime according to Table 2 in the Appendix, or be judged by the professionals on the feeding team as able to meet these behavioral skills by week 10 of the protocol.

4.2 Exclusion Criteria

Study enrollment will exclude potential subjects with any of the following conditions or taking any of the following medication:

1. Children receiving oral steroids.
2. Parent has a known developmental delay or cognitive impairment that may make participation in the study difficult (children with these issues will not be excluded).
3. Children receiving intensive (defined as more than one session per month) behavioral feeding therapy with a licensed psychologist (previous behavioral feeding therapy is not an exclusion criterion; neither is current oral-motor, sensory, or speech therapy).
4. Children of non-English speaking parents.

4.3 Subject Recruitment and Screening

Sixty subjects are needed for our analysis plan, so with a maximum of 20% drop out (which exceeds drop out from our previous work), a total sample of 72 will need to be recruited over the 5 year project (for more information see Sample Size Determination in Data Analysis Plan section). To allow for study start up and completion phases, we will need to recruit approximately 20 subjects per year when in active recruitment. Currently, the University of Kansas Medical Center team sees 12 new patients per month, Children's Mercy Hospital sees 12 new patients per month, University of California San Diego/Rady Children's Hospital sees 8 new patients per month, the New Orleans site sees 8 new patients per month, Arnold Palmer Hospital for Children sees 8 new patients per month, and Children's Hospital of Philadelphia sees 12 new patients per month, resulting in a total potential recruitment base of 60 feeding subjects per month across our primary sites. Based upon clinic data, 20% of the patients seen will meet inclusion/exclusion criteria (resulting in 12/month or 144/year). Of these, we predict that half will be given permission to participate, given the highly medically complex nature of many children with feeding problems (resulting in 72/year). Assuming that half of eligible families participate (36/year), current clinic volume at participating sites will result in successfully meeting recruitment goals.

Participants will be recruited by a pediatric healthcare provider or other members of the feeding team at each site. Sites will likely recruit through their multidisciplinary feeding teams, but may recruit from other clinics, patient registries, electronic medical records, and inpatient settings as appropriate. Methods of recruitment could include: approaching patients during routinely scheduled patient visits, sending letters, emails, or calling patients identified through and electronic medical record or other site specific patient registry, or emailing patients through the electronic medical record platform. Sites may also place recruitment flyers, informational videos, and information on their institution's local webpage or social media pages, affiliated research network pages (such as Pioneers Research Network at KUMC or other affiliated research center websites), post ads to social media and local media, and post flyers in the community or to online groups (such as social media or other sites that focus on feeding issues in children, parents of tube-fed children, etc.) If parents are interested in participating, they will have access to a toll free number to call with questions, or they may request to be contacted by entering their contact information in a REDCap survey. Our team members are experienced with each of these types of recruitment methods and many were used in our previously funded NIH study in feeding.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects will be considered "at risk" and reviewed by the medical monitor and site PI if either of the following two conditions. The medical monitor and site PI will determine if it is safe for the participant to continue in the study (or, under what conditions it may be safe for the participant to continue) given all patient characteristics, including baseline weight for height ratio or BMI percentile.

1) If more than 0.5 kg of weight is lost consistently per week over three consecutive weeks
2) If the subject experiences 10% loss of total body weight

Children who are removed from the study will be treated clinically.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws from the study, they will be asked to continue on with their assessments (at least height and weight and diet recall, at the very minimum). This will be done so we can have outcome on our primary endpoint even for subjects who withdraw. Unless a subject/parent actively refuses, we will try to contact them for these assessments via phone and email and if this fails, we will attempt to reach them via certified letter at their last known address.

5 Study Drug

5.1 Description

Megestrol

Megestrol is a steroid and progestational drug FDA approved for treating anorexia or weight loss in patients with acquired immunodeficiency syndrome. Its use in the current protocol is “off label” to stimulate appetite in tube-fed infants and toddlers who are weaning from tube feedings and learning to eat. The precise mechanism of action that leads to increased appetite and weight gain is unknown, but is probably related to megestrol’s glucocortocoid effect (41). Side effects of megestrol include suppression of the adrenal glands and new onset diabetes mellitus (41). These complications are minimized by limiting the duration of treatment to 6 weeks (41). Other side effects include heart failure, nausea and vomiting, edema,dyspnea, hyperglycemia, alopecia, hypertension, carpel tunnel syndrome, mood changes, malaise, asthenia, lethargy, sweating and rash (41). Megestrol’s safety and effectiveness have not been established in children. However, there are several pediatric trials with megestrol for anorexia or malnutrition (42-44). In a megestrol trial for children with cystic fibrosis, the youngest child treated was 6 months of age and treated with 10 mg megestrol/day (42). The proposed study will use megestrol 6 mg/kg/day in two doses because this dose has been effective and safe in two previous studies using megestrol to stimulate appetite in children transitioning from tube to oral feedings. (6,45). Megestrol will be dosed at 6 mg/kg/d at weeks 10-11, at 4 mg/kg/d at week 12, at 2 mg/kg/d at week 13, and fully tapered at the end of week 13. Megestrol is absorbed from the small bowel, so feeding it through the tube will be acceptable (41).

Placebo Group

Subjects randomized to the placebo protocol will receive a placebo syrup identical in taste and smell to megestrol at the same intervals as those in the megestrol group but the syrup will contain no active ingredients.

5.2 Treatment Regimen

Megestrol will be dosed based off their weight at the Week 10 visit, and dose will be rounded to the nearest 0.1 ml. Megestrol will be dosed at 6 mg/kg/d at weeks 10-11, at 4 mg/kg/d at week 12, at 2 mg/kg/d at week 13, and fully tapered at the end of week 13.

Equal doses will be taken twice daily. Subjects will be given instructions on when to take the medication and what to do if they miss a dose. If it has been < 6 hours since missing the dose, they should take the dose as soon as they remember. If it has been ≥ 6 hours since missing the dose, they should skip the dose. Subjects will be asked to document any skipped doses and report those to the study team at their next visit.

If a participant is removed from the study while taking the study drug, we will follow the drug tapering plan based on what what day they are in the treatment regimen:

- Day 1-14 Drug can be stopped at current dose.
- Day 15-18 Continue 4 mg/kg for a total of 3 days. Decrease to 2 mg/kg for 3 days and then stop.
- Day 19-21 Decrease to 2 mg/kg for 3 days and then stop.
- Day 22-23 Continue 2 mg/kg for a total of 3 days and then stop.
- Day 24-28 Stop drug.

Regardless of when the drug is stopped, a morning cortisol lab value will be taken 5 days after the final dose of study drug.

5.3 Method for Assigning Subjects to Treatment Groups

Patients will be randomized within each site at a 1:1 ratio into the treatment and placebo groups. The statistician will generate ten sets of randomization codes, and send one set of codes to the pharmacist of each site. All the other study personnel will be blinded to the result of randomization.

Preparation and Administration of Study Drug
The pharmacy at each site will prepare megestrol or placebo for each subject as dictated by the random codes prepared by the study statistician. The compound formula for each site will be identical, and the taste, look and smell of the placebo and megestrol will be matched.

Subject Compliance Monitoring
Subjects will be asked to report missed doses of study medication during their regularly scheduled clinic or tele-visits. If a patient is significantly noncompliant with medication (as evidenced by missing 7 or more days of dosage in a one month period) subjects will be counseled, and withdrawn from the study if unable to change.

5.4 Prior and Concomitant Therapy

All current therapies and medications will be allowed to continue throughout the study, except those listed in the exclusionary criteria section.

Parents will be educated that megestrol is a steroid, and what to do if their child becomes acutely ill and the treating provider prescribes a steroid. So, if the child is prescribed a steroid (oral or inhaled), the parents should consult with the treating physician to see if a non-steroidal option is available. If not, and the treating physician proceeds with steroids for medical reasons, the parent should contact the iKanEat study team to inform them of this prescription.

If the prescription is over 7 days, then the iKanEat medical monitor will review the case and decide how to proceed with the study drug. Options could include tapering off the study drug temporarily and to reactivate after the prescription is given; or, tapering early if the child is in the final weeks of study drug; or other options as deemed appropriate by the medical monitor.

If the prescription is 7 days or less, than the study team will note it in the REDCap Case Report Form and report it to the medical monitor, but no action will be taken.

5.5 Packaging

The drug will be placed in bottles and will be dispensed directly or from the investigational pharmacy.

5.6 Blinding of Study Drug

The drug will be dispensed by the investigational pharmacy at each site, who will be the only unblinded part of the team. They will receive the random codes prepared by the study statistician, and will dispense placebo/megestrol as appropriate.

5.6.1 Storage

The drug will be stored at room temperature in amber bottles.

5.6.2 Dispensing of Study Drug

The megestrol/placebo will be dispensed by each site's investigational pharmacy. Site pharmacists may round doses to the nearest 0.1 ml if not done previously by the investigator. Refer to the pharmacy manual for detailed instructions and a dosing table.

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form and signed and dated by a member of the study team.

6 Study Procedures

iKanEat Intervention

The 24 week iKanEat intervention is composed of 4 clinic visits and a series of approximately 14 (See Table 3. Procedures Timeline). Serious Adverse Events (SAEs) will be assessed at every point of contact.

Clinic Visits

Clinic visits will occur at each site (see Sites) in their clinical space. Each visit will involve obtaining weight and height (in triplicate, in light clothing), vital signs, and then speaking with a healthcare practitioner regarding overall health. The child will also receive a complete physical exam, similar to a routine pediatric visit, including blood pressure and temperature, and will also be assessed for side effects of the iKanEat protocol. All participants will complete a blood draw at weeks 10 and 14. Participants taking inhaled or intranasal steroids will take an additional blood draw at week 0. At the initial clinic visit a medical history will also be obtained.

Remote Clinical Visits

In the event clinics are closed (ie. COVID-19 outbreak) or when convenient for patients, clinical visits will be conducted remotely via the Zoom teleconferencing app. Any supplies needed (stool collection kits, scale, tape measures, iPad with data, etc.) will be mailed to the family in advance. If parents do not have a device compatible with the Zoom app, they will be loaned a device with a data plan. Parents will be trained on how to obtain height and weight at home. Digital scales and tape measures will be sent to the families (or they may use their own if they have them), and each family will measure the height and weight during a video call via Zoom app with an iKanEat team member to ensure measurement accuracy. Other vitals, such as blood pressure, pulse, and temperature will not be obtained remotely. Participants will be asked to collect a stool sample and store it in their home freezer until the sample can be obtained by iKanEat study personnel via FedEx shipping or drop-off at the local site.

Tele-Visits

Tele-visits will begin by building rapport and asking for a summary of all relevant information since the last point of contact, including parent perception of changes in weight, feeding habits, progress, stress of parent/child, and illness. Children will be assessed for side effects of the iKanEat protocol at every tele-visit per parent report. The majority of the time left in the 30 minute session will be spent dealing with parent concerns, which our previous project indicates may include questions about measures, questions about implementation of the iKanEat protocol, and ensuring that children/families adhere to the oral-motor and behavioral guidelines for feeding (see Table 1 and 2). Specifically, we will assess for the presence of daily mealtimes (at least 3-5 times per day), limited grazing between planned meals/snacks, consistent mealtime location, appropriate meal length (approx. 20 minutes), and limited distractions during mealtime (refrain from use of TV, iPad, toys, etc.). Families will also be encouraged to engage in family mealtime together, to prohibit force feeding across all feeders, and to focus on positive parent behavior, positive meal demeanor, and appropriate food presentation (as defined in Table 2). Motivational interviewing and cognitive behavioral parent training techniques will be used to improve parent performance on these skill areas. These skills will rely heavily on the detailed training manuals available from The Incredible Years, and our therapists will specifically use the materials from the book “Collaborating with Parents to Reduce

Children's Behavior Problems: A book for Therapists Using the Incredible Years Programs." The structure and content of these tele-visits is based directly on those used in our prior work (HD066629). All visits (clinic and tele-visits) will focus directly on the oral-motor and behavioral skills necessary for oral eating.

Tele technology

Parents will be allowed to choose if they wish to receive their tele-visits over phone (as we did in our previous work) or via interactive televideo (such as Skype or Facetime). For patients who choose to do the visits over phone, we will provide a toll free number with a fully secure connection. For patients who choose to use the tele-visit option, KUMC also has access to the Zoom Mobile Meeting Platform which provides a secure videoconference bridge. These point-to-point connections are highly secure, meaning there is no concern about the release of protected health information. The Zoom platform also allows for the connection of diverse types of systems, including mobile devices, desktop computers, and established telehealth equipment in many clinical settings (important for eventual dissemination, if appropriate). The Zoom app or a similar secure technology will be utilized to connect participants to the researchers for all study procedures. No matter whether patients chose to receive their tele-visits over phone or interactive televideo, they will be using their own existing device, such as a home phone, cell phone, desktop computer or tablet device, a study-owned device that is loaned to the participant. Tele-visits will be recorded to ensure interventionist adhere to the treatment manual and for patient care purposes.

Interventionists

Interventionists for the clinic visits will be pediatric healthcare providers accompanied by study team staff at each site (see letters of support). These providers are experts in feeding and serve as the physicians and/or Medical Directors of the feeding programs at their sites (see letters of support). Interventionists for the tele-visits will be behavioral experts at the University of Kansas Medical Center and are trained multidisciplinary feeding team members with telehealth experience, including two PhD level psychologists (Davis, Bruce), and a research dietitian who worked with the team as an interventionist on the previous study. All behavioral interventionists are trained in motivational interviewing and in cognitive behavioral parent training and are familiar with The Incredible Years program that will serve as a basis for the behavioral parent training program used here.

Fidelity

Treatment fidelity for tele-visits will be measured by having a Graduate Research Assistant code a randomly selected sample of 10% of all intervention sessions (via video recording). They will code for adherence to the visit checklist. The recordings will be selected and coded via a random numbers table.

6.1 Pre-Screening Session (-14 to -1 day before Week 0)

Participants will be identified through ongoing multidisciplinary feeding teams at the participating sites. Pre-screening sessions will occur within a regularly scheduled clinical care visit. The study team will evaluate the patient for eligibility, and families will be invited to participate and consent forms signed.

If approved, electronic consent will occur in person during a regularly scheduled clinic visit. A member of the study team will pull up the consent document on tablet and review the form with the participant. The participant and study personnel will sign the document by finger or stylus. After the consent form is submitted, the study personnel will receive a prompt in REDCap to print a pdf copy of the signed consent and give to the participant during the visit. The study personnel will also have the option to email a copy of the consent to the participant directly from REDCap. As this is a multi-site study, the e-consent process will be done in accordance with state laws of the participating site.

If the consenting visit is conducted remotely, the study team will have the option of doing the e-consent over a tele-video call (Zoom). In this case, the REDCap e-Consent template will be modified so that the parent can open the parent signature e-Consent page on their device during the Zoom call. After the consent discussion, the parent will sign their REDCap signature form and submit. The study personnel will sign the study personnel signature form on their device and save. The participant will be provided with a copy of the consent form as well as the signature pages of both the parent and study personnel.

Alternatively, a paper consent can be obtained. The study team will access the latest consent form from REDCap, print it, and proceed with the consent discussion with family. Once the consent has been fully executed, a copy will be provided to the family and uploaded to REDCap.

After consent is obtained, measures will be completed by the parent in the REDCap (PIP, ITQOL or CHQ, RAND SF-36, PedsQL). Parents will be asked for 3 days/times when research staff can call them to complete the three 24 hour dietary phone recalls (24hr DR). Participants will be given a supplies for the 4 stool collections and be asked to collect the sample at home 1-7 days prior to each clinic visit (Week 0, 10, 14, 24), store in their home freezer, and return the sample at their study visit. Families will be scheduled for their first study visit in approximately 1 to 14 days.

6.2 Clinic Visit 1 (Week 0)

Participants will be given a full medical history and exam (including vital signs). Height and weight will both be taken in triplicate via calibrated equipment by a trained staff member. Participants taking inhaled or internasal steroids will complete a blood draw (morning cortisol). Participants who are <u>not</u> taking inhaled or intranasal steroids will not complete a blood draw during the Week 0 visit. If an abnormal morning cortisol value is measured, follow the redraw procedures under section 3.4 Primary Safety Endpoints. Participants will bring in a frozen stool sample. Subjects will remain on their current G or G/J tube feeding regimen as determined by their clinical feeding team. If patient is volume sensitive, the feeding team may intervene clinically by placing the subject on continuous feeds when indicated. Families will be encouraged to contact team members with questions or concerns at any time throughout the study period. Participants who complete the measures at pre-screening and complete Clinic Visit 1 will be randomized to an intervention by the study statistician. Participants will be asked measure the child's weight using a digital home weight scale. If the family does not have a digital weight scale, one will be provided to them.

6.3 Tele-Visit (Weeks 1, 3, 5, 7, 9)

Participants will complete a tele-visit with a member of the study team to discuss parent perception of changes in weight, feeding habits, progress, stress of parent/child, and illness. Participants will be asked to measure the child's weight using a digital home weight scale. Families will be encouraged to contact team members with questions or concerns at any time throughout the study period.

6.4 Clinic Visit 2 (Week 10)

Participants will return to clinic to complete vital signs and blood draw (morning cortisol). If an abnormal morning cortisol value is measured, follow the redraw procedures under section 3.4 Primary Safety Endpoints. Height and weight will both be taken in triplicate via calibrated equipment by a trained staff member. Participants will bring in a frozen stool sample. Patients will be given megestrol or placebo, but asked to wait to administer the 1st dose until lab value for morning cortisol are confirmed normal. Megestrol will be dosed at 6 mg/kg/d at weeks 10-11, at 4 mg/kg/d at week 12, at 2 mg/kg/d at week 13, and fully tapered at the end of week 13. Participants will be asked to complete the PIP, ITQOL or CHQ, RAND SF-36, PedsQL and schedule three 24 hr Dietary recall phone calls over the coming week. Five

days after the clinic visit, parents will begin to taper G or G/J tube feedings by 10% each day until they are stopped altogether. Families will be encouraged to contact team members with questions or concerns at any time throughout the study period.

6.5 Tele-Visit (Week 11)

Participants will complete a tele-visit with a member of the study team to discuss the child's response to treatment, parent perception of changes in weight, feeding habits, progress, stress of parent/child, and illness. Participants will be asked to measure the child's weight using a digital home weight scale. Megestrol will be continued daily at the full dose. Parents will be asked about any major changes in their health, appetite, and medications. Families will be encouraged to contact team members with questions or concerns at any time throughout the study period.

6.6 Tele-Visit (Week 12)

Participants will complete a tele-visit with a member of the study team to discuss the child's response to treatment, parent perception of changes in weight, feeding habits, progress, stress of parent/child, and illness. Participants will be asked to measure the child's weight using a digital home weight scale. Megestrol will be continued daily at 4 mg/kg/d Parents will be asked about any major changes in their health, appetite, and medications Families will be encouraged to contact team members with questions or concerns at any time throughout the study period.

6.7 Tele-Visit (Week 13)

Participants will complete a tele-visit with a member of the study team to discuss the child's response to treatment, parent perception of changes in weight, feeding habits, progress, stress of parent/child, and illness. Participants will be asked to measure the child's weight using a digital home weight scale. Megestrol will be continued daily at 2 mg/kg/d. Parents will be asked about any major changes in their health, appetite, and medications. Families will be encouraged to contact team members with questions or concerns at any time throughout the study period.

6.8 Clinic Visit 3 (Week 14)

Participants will return to clinic to complete vital signs and blood draw (morning cortisol). The morning cortisol lab value must be taken at least 5 days after the final dose of study drug, so verify with the family when the last dose will be taken before scheduling the Week 14 visit. If an abnormal morning cortisol value is measured, follow the redraw procedures under section 3.4 Primary Safety Endpoints. Height and weight will both be taken in triplicate via calibrated equipment by a trained staff member. At the visit they will also complete the PIP, ITQOL or CHQ, RAND SF-36, PedsQL and schedule three 24 hr Dietary recall phone calls over the coming week. Participants will bring in a frozen stool sample. Tube feedings and megestrol will have ceased. Parents will be asked about any major changes in their health, appetite, and medications

6.9 Tele-Visit (Week 14)

Participants will complete a tele-visit with a member of the study team to discuss parent perception of changes in weight, feeding habits, progress, stress of parent/child, and illness. Participants will be asked

to measure the child's weight using a digital home weight scale. Families will be encouraged to contact team members with questions or concerns at any time throughout the study period

6.10 Tele-Visits (Weeks 15, 17, 19, 21, 23)

Participants will complete a tele-visit with a member of the study team to discuss parent perception of changes in weight, feeding habits, progress, stress of parent/child, and illness. Participants will be asked to measure the child's weight using a digital home weight scale. Families will be encouraged to contact team members with questions or concerns at any time throughout the study period.

6.11 Clinic Visit 4 (Week 24)

Participants will return to clinic to complete vital signs and measures (PIP, ITQOL or CHQ, RAND SF-36, PedsQL) and schedule three 24 hr Dietary recall phone calls over the coming week. Participants will bring in a frozen stool sample. Families will be encouraged to contact team members with questions or concerns at any time throughout the study period.

At every clinic visit and tele-visit we will record and evaluate concomitant medications. Also, if any safety concerns are noted at any clinic or tele-visit, additional visits may occur. Should any clinical concerns be noted, appropriate medical/clinical treatments will also occur as necessary. If any serious adverse events occur (as outlined elsewhere), providers will be unblinded to the subject's group, the subject will be removed from the study and patients will receive all necessary treatment clinically.

7 Statistical Plan

7.1 Sample Size Determination and Statistical Methods

For Aim1 (To assess the efficacy of megestrol as part of the 24 week iKanEat protocol), if at least 90% of the treatment group successfully transitions (in pilot 100% successfully transitioned), with 72 participants, we would have .80 power to detect an odds ratio of .21. With 60 participants, we would have power to detect an odds ratio of .18. If only 75% of the treatment group successfully transitions, we will still have .80 power to detect an odds ratio of .25 with our smallest expected sample size of 60.

For Aim 2 (To assess the safety of megestrol as part of the 24 week iKanEat protocol), all analyses are descriptive, so a power analysis is not conducted.

For Aim 3 (To examine the effect of the transition from tube to oral feeding on parent stress and parent and child quality of life), with 60 participants, we would have .78 power to detect differences in slopes over the four data points equivalent to a standardized effect size of d=.75 or larger. With a sample size of 72, there will be .80 power to detect a difference in slopes equivalent to a standardized effect size of .70. To answer those questions in which the grouping factor is success in treatment, such as 3A (The transition to oral feeding will temporarily increase parent stress at week 14 at the cessation of tube feeding, with a return to baseline by week 24) and 3B (The transition to oral feeding will increase parent/child quality of life at 24 weeks compared to week 0), assuming that 60% of the participants across groups are successful, we would have sufficient power to detect effects equivalent to a standardized effect size of d=.42 or larger. With a sample size of 60, the minimum detectable effect size would increase to d=.59. If 70% percent are successful, with 72 participants we can detect effects equivalent to d=.61, and with 60 participants d=.70. These are moderate sized effects.

Planned Analyses

To address Aim 1, analyses will be conducted using Generalized Linear Mixed Models with a logit link within SAS Proc GLIMMIX to model the binary outcome of transitioned to oral feeding (y/n) defined as at least 90 percent of calories consumed orally. Fixed effects (dummy variables) will be entered for each site as described by McNeish and Stapleton (2016) to account for the clustering of the participants within sites. This will result in essentially, a logistic regression model with appropriate standard errors. Sex, age at initiation, treatment condition, and interactions with treatment condition will enable us to examine the effect of group assignment on successful transition to oral feeding by week 24. Interactions between treatment group and sex will be examined but will not be sufficiently powered to reach definitive conclusions about sex differences. In addition to overall effects, subgroup analyses will be reported for males and females to examine treatment effects within sex groups.

To address Aim 2, we will determine whether any of our participants in either group have adrenal sufficiency levels outside of the normal range at any time point. Should any participant have levels outside of the normal range, we will descriptively examine the individual characteristics associated with this, including group assignment, medical diagnoses, sex, and age at initiation. These characteristics will be reported descriptively.

To address Aim 3, we will model parent stress levels, child quality of life, and parent quality of life for participants in both treatment conditions over the four measurement occasions using General Linear Mixed Models. As in Aim 1, fixed effects for site will be added to the model as will sex and age at initiation. Once the shape of the trajectory over time has been modeled, a successful transition to oral feeding indicator, defined as consuming 90% or more of calories orally, will be added to the model at level 2. For 3A, the primary variable of interest will be the time by successful transition interaction on parental stress level. Estimate statements will examine group differences in stress at week 14 and 24. To address hypothesis 3B regarding Quality of Life outcomes, we will initially model the trajectory over time for each outcome with the same set of predictors as in 3A. Of primary interest will be the time by successful transition interaction on subscales for parental quality of life and the parent impact time, general health perceptions, growth and development, and parent impact emotional subscales for child quality of life which showed the greatest response to intervention in our pilot data. It is expected that some subscales such as general health perceptions and parent impact time will show more response to intervention than others. A significant positive slope for some quality of life indicators are hypothesized for those children who transition to oral feeding while stable or declining quality of life ratings are expected for those who are unable to transition to oral feeding. Finally, to complete our analyses of sex as a biological variable (SABV) we will assess study outcomes by gender.

To address Aim 4, the Shannon Index[60] will be used to determine microbial diversity. Data analysis will be completed using the paired t-test unless the data is not normally distributed in which case analysis will be completed with the Wilcoxon Signed Rank test to compare the index values of patients on each diet.

Heterogeneity of Subjects

Children with enteral feeding requirements are diverse in their presenting medical problems (cardiac, developmental delays, post-prematurity, cerebral palsy, etc.). If the subject group in this study was more homogenous, it would be easier to determine efficacy of the protocol. However, because we have opted to select a more heterogeneous group, the external validity of this study will be high, making our results highly generalizable to other children in clinical need.

Multi-site

The current study is proposed at several sites in order to recruit the number of children who meet the specific inclusion/exclusion criteria. Conducting a multi-site study can present hurdles. However, many of the investigators have worked together previously on feeding studies (HD068221) and publications. To

minimize any differences across sites, the PI will travel to each site annually, and the team will meet together every year at the NASPGHAN meeting. Also, a weekly mandatory one hour phone conference will occur across all sites to discuss protocol implementation issues.

Study Locations

Sites that have agreed to participate include the University of Kansas Medical Center (Almadhoun, Bruce, Davis), Children's Mercy Hospital (Edwards, Cocjin), University of California San Diego/Rady Children's Hospital (Mousa), New Orleans Children's Hospital (Hyman), Arnold Palmer Hospital for Children (Mehta), Children's Hospital of Philadelphia (Cohen), and Boston Children's Hospital (Rosen). Additional sites available for recruitment, if the current sites fall behind in their recruitment goals, include the sites of our Data Safety Monitoring Board Members, and sites that are members of the newly formed National Feeding Consortium (of which the PI and several site PIs are members). See letters of support for more information. Sites will all have an existing multidisciplinary feeding team that includes at least a pediatric healthcare provider (MD, DO, ARNP), Psychologist, Dietitian, and Occupational Therapist/Speech Pathologist, as recommended by experts (1).

Coordinating site

The University of Kansas Medical Center will be the lead and coordinating site. Research data will be entered by the sites into a REDCap data capture system managed by KUMC study team.

Pharmacy

The investigational pharmacy at Children's Mercy Hospital will coordinate with each site their purchase of the megestrol solution from the single manufacturer. All sites will use the exact formulation, containers, and instructions as specified by the lead investigational pharmacy.

Single IRB Review for a Multi-site study

KUMC will serve as the IRB of record for all sites. Procedures will be identical at all sites. Sites will all have an existing multidisciplinary feeding team that includes at least a pediatric healthcare provider (MD, DO, ARNP), Psychologist, Dietitian, and Occupational Therapist/Speech Pathologist.

The PI and study coordinator will have an orientation with each site prior to enrolling subjects. The study coordinator will be responsible for notifying all sites of amendments to the IRB and dissemination of current study documents (please see Multi-Site Communication Plan).

To minimize any differences across sites, the PI will travel to each site annually, and the team will meet together every year at the NASPGHAN meeting. Also, a weekly mandatory one hour phone conference will occur across all sites to discuss protocol implementation issues. The study coordinator will send communication to the PI and the Point of Contact (POC) at each site of any relevant study communication (please see Multi-Site Communication Plan).

Protocol compliance, problems, and adverse events will be discussed in the weekly multi-site conference call. Sites will be given written protocols during orientation that define protocol deviations, unanticipated problems, and adverse events, and the method to report those to the lead site.

Safety

For the treatment arm of the current study we are proposing to use medications off label. Therefore there is risk of unexpected negative results. We do not expect any negative outcomes, however, as these medications have been used safely in previous work (12,13). To monitor for these negative side effects,

patients will be contacted weekly while taking the medication (via the Tele-visits described previously) for any negative gastrointestinal, behavioral, feeding, or other negative sequelae suspected to result from the medications. (If such patients are subjected to stress such as an infection or surgery, they may develop adrenal crisis. The patient suddenly becomes cyanotic and cold, blood pressure drops, and without immediate resuscitation the patient goes into shock). If any negative outcomes are identified they will be reported to our Data Safety and Monitoring Board and proper steps will be taken.

Under certain conditions children may removed from the study and treated clinically. The medical monitor and site PI will assess the case and determine if it is safe for the participant to continue.

Risk/benefit assessment:

Our previous work suggests that iKanEat is effective in moving children from tube to oral eating, and that amitriptyline does not improve the outcomes associated with the protocol. However, we do not know if the remaining medication (megestrol) improves the outcomes associated with iKanEat. As all medications have risks, it is necessary to test this remaining medication to determine if the risk is outweighed by the benefit the medication brings to the iKanEat protocol.

Data Safety Monitoring Board

For the current study we will have a Data Safety Monitoring Board that will review all subject safety data twice annually. DSMB will review protocol adherence, adverse events, unanticipated problems, voluntary and study team initiated withdrawals, etc. This team is available to the investigators at any time should an issue of safety arise, as was the DSMB for their previous study (HD068221). This board will be composed of Dr. Susan Orenstein, Professor of Pediatrics and Dr. Jeannie S. Huang, Professor, Rady Children's Hospital and UCSD. Twice annual conference calls will be held between the DSMB members and the investigation team to assure the best outcome for all subjects. Any serious adverse events will be reported immediately to the relevant institutional IRBs and to the DSMB.

Population(s) for Analysis. Our primary analysis will focus on a protocol-compliant population, but we will secondarily also analyses the all-treated population, as described below.

- All-randomized population: Any subject randomized into the study, regardless of whether they received study drug
- All-treated population: Any subject randomized into the study that received at least one dose of study drug
- Protocol-compliant population: Any subject who was randomized and received the protocol required study drug exposure and required protocol processing

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

For the current study, we will use CTCAE criteria, incorporating the additional considerations about pediatric effects and regarding hospitalization. Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has

discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
For the current study, we will use CTCAE criteria, incorporating the additional considerations about pediatric effects and regarding hospitalization. Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Expected and Unexpected event criteria
Side effects of megestrol affect up to 5% of adults and older children. Those expected side effects include:

- Diarrhea
- Rash
- Gas
- High blood pressure
- Weakness
- Trouble sleeping
- Nausea
- Low levels of oxygen in the blood causing pall skin color and sleepiness
- Adrenal insufficiency (pale skin color, cold to the touch, weight loss, thirsty, dizzy or disoriented)
- Fever
- Stomach pain and discomfort
- Heartburn
- High levels of sugar in the blood, which can cause tiredness, blurry vision, increased thirst and hunger, and passing urine often.
- Headache
- Pain
- Vomiting
- Pneumonia
- Urinary Frequency

All events (expected or unexpected) will be logged and reported to the lead PI, Dr. Ann Davis and the Medical Monitor, Dr. Hayat Mousa. Side effects other than those listed above would be considered unexpected and would be also reported to the IRB. If an expected event is happening at a higher rate than anticipated (>5% of patients), the IRB must also be notified.

If medical or psychosocial concerns occur during week 1-9 that do not meet the criteria for subject withdraw, but negatively affect the subject's feeding routine, the PI and the Medical Monitor may pause the protocol until the patient regains feeding stability. The subject will resume the protocol if the feeding interruption is short-term (2 weeks to 6 months). For long-term feeding interruptions (>6 months), the subject may start the protocol over at week 0.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the investigator sponsor

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to Ann Davis by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to: Ann Davis, PhD, MPH, ABPP (email, adavis6@kumc.edu, Fax 913-588-2253, Phone 913-588-5928 or 24 hours 913-588-5000).

Within 48 hours of the report, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed

Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

8.3.2 Investigator reporting: notifying the IRB

Investigators are responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 5 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days***
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening, and

- ***Within 15 calendar days***
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

-or-

– a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Any finding from tests in laboratory animals that:

– suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

8.3.3 Sponsor reporting: Notifying participating investigators

It is the responsibility of the study sponsor to notify all participating investigators of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects.

8.4 Unblinding Procedures

Each investigator must inform the sponsor of all subjects whose treatment was unblinded within 24 hours of such unblinding. We anticipate that in most cases, the unblinding will be part of managing an SAE, and will be reported with the SAE, however, in cases where unblinding was not associated with an SAE, such actions should be reported within one week.

At the completion of the study, participants will be contacted to notify them of their treatment assignment.

8.5 Stopping Rules

If 2 out of the first 20 patients have a grade 3 event related to the study, we will stop or modify the study; if 1 subject has a grade 4 event related to the study, we will stop the study. After a stop the study will only re-start after a thorough review and uniform agreement by the investigators and the DSMB.

8.6 Medical Monitoring

It is the responsibility of the Site Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). The medical monitor will review all reported adverse events and regularly assess the number and type of serious adverse events.

8.6.1 Independent Data and Safety Monitoring Board

For the current study we will have a Data Safety Monitoring Board that will review all subject safety data twice annually. This team is available to the investigators at any time should an issue of safety arise, as was the DSMB for their previous study (HD068221). This board will be composed of Dr. Susan Orenstein, Professor of Pediatrics, University of Pittsburgh School of Medicine and Dr. Jeannie S. Huang, Professor, Rady Children's Hospital and UCSD. Twice annual conference calls will be held between the DSMB members and the investigation team to assure the best outcome for all subjects.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). 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 to collect or use PHI, 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 to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.5 Data Management and Security

Site PI and site study coordinators will have access to their own site's data. The lead PI and study team will have access to data from all sites. Sites will not have access to other site's identified data. Deidentified aggregate data may be shared for safety monitoring during site conference calls and to the DSMB. Children's Mercy's Investigational Pharmacy will have access to identified data from each site for drug randomization.

Data will be shared from the sites to the coordinating site via REDCap or secure file transfer. Data will be saved onto secured shared drives at KUMC and on shared drives at the site's home institutions. KUMC will retain the data for 10 years after the completion of the study or once subjects turn 18 years old.

Identifiable information will be collected. Information will be coded with a subject ID and identifiers will be removed to a linking list that will be saved in a separate location. Lead PI and study coordinator will have access to all coded data. Site PI and coordinators will have access to the linking log for their site only. Identified data will be located in REDCap. Once data is abstracted from REDCap, it will be saved on the KUMC shared drives where identifiers will be removed and placed into a linking log. Identifiable data will be sent from the site to KUMC using secure file transfer.

Data will be stored in REDCap and on KUMC secure shared drives. Consent will be obtained electronically via REDCap. REDCap may be brought up on a mobile device for participants to complete, however, no data will be stored directly on the mobile device.

9.6 Specimen collection

Blood samples will be collected during the clinic visit and sent to the lab for processing. Stool samples will be split in half, with part of the sample being sent to Novogene for processing. The other half of the sample will be retained at the site until processing at Novogene is complete. After processing, the specimens will be destroyed, and nothing will be retained.

9.7 Quality Assurance and Monitoring

Data will be collected using REDCap, which allows us to make responses required to ensure complete data. Study coordinators will verify the data during the clinic visit to ensure data collection was accurate and complete.

10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachments for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Study Finances

11.1 Funding Source

This study is financed through a grant from the National Institutes of Health, Eunice Kennedy Schriver National Institute of Child Health & Human Development.

11.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study.

11.3 Subject Stipends or Payments

Subjects who consent to the protocol (either in the megestrol or placebo group) will be offered approximately $100 for each Clinic Visit (Week 0, 10, 14, 24) to reimburse them for transportation, filling out measures, and any other costs they encounter. Total possible payment is $400 if all clinic visits and measures are completed.

12 References

1. Manikam R, Perman JA. Pediatric feeding disorders. J. Clin. Gastroenterol. Jan 2000;30(1):34-46.
2. Rommel N, De Meyer AM, Feenstra L, Veereman-Wauters G. The complexity of feeding problems in 700 infants and young children presenting to a tertiary care institution. J. Pediatr. Gastroenterol. Nutr. Jul 2003;37(1):75-84.
3. Stephens BE, Vohr BR. Neurodevelopmental outcome of the premature infant. Pediatr. Clin. North Am. Jun 2009;56(3):631-646, Table of Contents.
4. Rudolph CD, Link DT. Feeding disorders in infants and children. Pediatr. Clin. North Am. Feb 2002;49(1):97-112, vi.
5. Staiano A. Food refusal in toddlers with chronic diseases. J. Pediatr. Gastroenterol. Nutr. Sep 2003;37(3):225-227.
6. Zangen T, Ciarla C, Zangen S, et al. Gastrointestinal motility and sensory abnormalities may contribute to food refusal in medically fragile toddlers. J. Pediatr. Gastroenterol. Nutr. Sep 2003;37(3):287-293.
7. Mason SJ, Harris G, Blissett J. Tube feeding in infancy: implications for the development of normal eating and drinking skills. Dysphagia. Winter 2005;20(1):46-61.
8. Senez C, Guys JM, Mancini J, Paz Paredes A, Lena G, Choux M. Weaning children from tube to oral feeding. Childs Nerv. Syst. Oct 1996;12(10):590-594.
9. Byars KC, Burklow KA, Ferguson K, O'Flaherty T, Santoro K, Kaul A. A multicomponent behavioral program for oral aversion in children dependent on gastrostomy feedings. J. Pediatr. Gastroenterol. Nutr. Oct 2003;37(4):473-480.
10. Clawson EP, Kuchinski KS, Bach R. Use of behavioral interventions and parent education to address feeding difficulties in young children with spastic diplegic cerebral palsy. NeuroRehabilitation.2007;22(5):397-406.
11. Davis AM, Dean K, Mousa H, et al. A Randomized Controlled Trial of an Outpatient Protocol for Transitioning Children from Tube to Oral Feeding: No Need for Amitriptyline. J. Pediatr. May 2016;172:136-141.e132. PMC4846510.
12. Cuvelier GD, Baker TJ, Peddie EF, et al. A randomized, double-blind, placebo-controlled clinical trial of megestrol acetate as an appetite stimulant in children with weight loss due to cancer and/or cancer therapy. Pediatr. Blood Cancer. Apr 2014;61(4):672-679.
13. Couluris M, Mayer JL, Freyer DR, Sandler E, Xu P, Krischer JP. The effect of cyproheptadine hydrochloride (periactin) and megestrol acetate (megace) on weight in children with cancer/treatment-related cachexia. J. Pediatr. Hematol. Oncol. Nov 2008;30(11):791-797.
14. Orme LM, Bond JD, Humphrey MS, et al. Megestrol acetate in pediatric oncology patients may lead to severe, symptomatic adrenal suppression. Cancer. Jul 15 2003;98(2):397-405.
15. Benoit D, Wang EE, Zlotkin SH. Discontinuation of enterostomy tube feeding by behavioral treatment in early childhood: a randomized controlled trial. J. Pediatr. Oct 2000;137(4):498-503.
16. Dunbar SB, Jarvis AH, Breyer M. The transition from nonoral to oral feeding in children. Am. J. Occup. Ther. May 1991;45(5):402-408.
17. Gutentag S, Hammer D. Shaping oral feeding in a gastronomy tube-dependent child in natural settings. Behav. Modif. Jul 2000;24(3):395-410.50. Megace RxMed: Pharmaceutical Information.
18. http://www.rxmed.com/b.main/b2.pharmaceutical/b2.prescribe.html39: 800-812.18. Luiselli JK. Cueing, demand fading, and positive reinforcement to establish self-feeding and oral consumption in a child with chronic food refusal. Behav. Modif. Jul 2000;24(3):348-358.
19. Burklow KA, Phelps AN, Schultz JR, McConnell K, Rudolph C. Classifying complex pediatric feeding disorders. J. Pediatr. Gastroenterol. Nutr. Aug 1998;27(2):143-147.
20. Thorne SE, Radford MJ, Armstrong EA. Long-term gastrostomy in children: caregiver coping. Gastroenterol. Nurs. Mar-Apr 1997;20(2):46-53.

21. Brotherton AM, Abbott J, Aggett PJ. The impact of percutaneous endoscopic gastrostomy feeding in children; the parental perspective. Child Care Health Dev. Sep 2007;33(5):539-546.
22. Pedersen SD, Parsons HG, Dewey D. Stress levels experienced by the parents of enterally fed children. Child Care Health Dev. Sep 2004;30(5):507-513.
23. Sullivan PB, Juszczak E, Bachlet AM, et al. Impact of gastrostomy tube feeding on the quality of life of carers of children with cerebral palsy. Dev. Med. Child Neurol. Dec 2004;46(12):796-800.
24. Michaelis CA, Warzak WJ, Stanek K, Van Riper C. Parental and professional perceptions of problems associated with long-term pediatric home tube feeding. J. Am. Diet. Assoc. Oct 1992;92(10):1235-1238.
25. Edwards S, Davis AM, Ernst L, et al. Interdisciplinary Strategies for Treating Oral Aversions in Children. JPEN J. Parenter. Enteral Nutr. Nov 2015;39(8):899-909. No PMCID.
26. Li J, Winkler M. Decompensated septic shock in the setting of megace-induced severe adrenal suppression in an otherwise healthy pediatric patient: a case report. Pediatr. Emerg. Care. Aug 2012;28(8):802-804.
27. Burklow KA, McGrath AM, Valerius KS, Rudolph C. Relationship between feeding difficulties, medical complexity, and gestational age. Nutr. Clin. Pract. Dec 2002;17(6):373-378.
28. Burklow KA, McGrath AM, Allred KE, Rudolph CD. Parent perceptions of mealtime behaviors in children fed enterally. Nutr. Clin. Pract. Oct 2002;17(5):291-295.
29. Davis AM, Bruce AS, Khasawneh R, Schulz T, Fox C, Dunn W. Sensory processing issues in young children presenting to an outpatient feeding clinic. J. Pediatr. Gastroenterol. Nutr. Feb 2013;56(2):156-160. PMC3548963.
30. Davis AM, Bruce AS, Mangiaracina C, Schulz T, Hyman P. Moving from tube to oral feeding in medically fragile nonverbal toddlers. J. Pediatr. Gastroenterol. Nutr. Aug 2009;49(2):233-236. PMCID: 2716418.
31. RXmed, Megace. http://www.rxmed.com/b.main/b2.pharmaceutical/b2.prescribe.html.
32. Marchand V, Baker SS, Stark TJ, Baker RD. Randomized, double-blind, placebo-controlled pilot trial of megestrol acetate in malnourished children with cystic fibrosis. J. Pediatr. Gastroenterol. Nutr. Sep 2000;31(3):264-269.
33. Eubanks V, Koppersmith N, Wooldridge N, et al. Effects of megestrol acetate on weight gain, body composition, and pulmonary function in patients with cystic fibrosis. J. Pediatr. Apr 2002;140(4):439-444.
34. Davis AM, Edwards S, Bruce A, et al. Moving from tube to oral feeding in medically fragile non-verbal toddlers: initial findings from a randomized controlled trial. Annual Meeting of the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition; 2013; Chicago, IL. No PMCID.
35. Frank GC, Berenson GS, Schilling PE, Moore MC. Adapting the 24-hr. recall for epidemiologic studies of school children. J. Am. Diet. Assoc. Jul 1977;71(1):26-31.
36. Streisand R, Braniecki S, Tercyak KP, Kazak AE. Childhood illness-related parenting stress: the pediatric inventory for parents. J. Pediatr. Psychol. Apr-May 2001;26(3):155-162.
37. Landgraf JM, Vogel I, Oostenbrink R, van Baar ME, Raat H. Parent-reported health outcomes in infants/toddlers: measurement properties and clinical validity of the ITQOL-SF47. Qual. Life Res. Apr 2013;22(3):635-646.
38. Yamada A, Kato M, Suzuki M, et al. Quality of life of parents raising children with pervasive developmental disorders. BMC Psychiatry. Aug 20 2012;12:119.
39. Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's manual for the SF-36v2 Health Survey. Quality Metric; 2008.
40. Merhar SL, Pentiuk SP, Mukkada VA, Meinzen-Derr J, Kaul A, Butler DR. A retrospective review of cyproheptadine for feeding intolerance in children less than three years of age: effects and side effects. Acta Paediatr. Aug 2016;105(8):967-970.
41. Megace RxMed: Pharmaceutical Information http://www.rxmed.com/b.main/b2.pharmaceutical/b2.prescribe.html
42. Marchand V, Baker SS, Stark TJ, Baker RD. Randomized, double-blind, placebo-controlled pilot trial of megestrol acetate in malnourished children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2000; 31:264-269.
43. Eubanks V, Koppersmith N, Woolridge N, et al. Effects of megestrol acetate on weight gain, body composition, and pulmonary function in patients with cystic fibroisis. *J Pediatr* 2002; 140:439-444.

44. Couluris M, Mayer JLR, Freyer DR, Sandler E, Xu P, Krischer JP. Effect of cyproheptadine and megestrol on weight in children with cancer treatment related cachexia. *J Pediatr Hematol Oncol* 2008;
45. Davis AM, Bruce AS, Mangiaracina C, Schulz T, Hyman PE. Moving from tube to oral feeding in medically fragile nonverbal toddlers. *J Pediatr Gastroenterol Nutr* 2009; 49:233-236.

46. Pentiuk S, O'Flaherty T, Santoro K, et al. Pureed by gastrostomy tube diet improves gagging and retching in children with fundoplication. *JPEN* 2011:35: 375.
47. Gallagher K, Flint A, Mouzaki M et al. Blenderized enteral nutrition diet study: feasibility, clinical and microbiome outcomes of providing blenderized feeds through a gastric tube in a medically complex feeding population. *JPEN.* 2018:42(6): 1046-1050.
48. Zoetendal EG, Vaughan EE and de Vos WM. A microbial world w Pentiuk S, O'Flaherty T, Santoro K, et al. Pureed by gastrostomy tube diet improves gagging and retching in children with fundoplication. JPEN 2011:35: 375.
49. Gallagher K, Flint A, Mouzaki M et al. Blenderized enteral nutrition diet study: feasibility, clinical and microbiome outcomes of providing blenderized feeds through a gastric tube in a medically complex feeding population. JPEN. 2018:42(6): 1046-1050.
50. Zoetendal EG, Vaughan EE and de Vos WM. A microbial world within us. Molecular Microbiology. 2006 59(6); 1639-1650.
51. Scott KP, Gratz SW, Sheridan PO, et al. The Influence of Diet on the Gut Microbiota. Pharmacological Research. 2013, 69: 52-60.
52. Voreades N, Kozil A and Weir TL. Diet and the development of the human intestinal microbiome. Frontiers in Microbiology. September 2014 5 (494).
53. Wu GD, Chen J, Hoffmann C, et al. Linking Long-term Dietary Patterns with Gut Microbial Enterotypes. Science. 2011 334(6052): 105-108.
54. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. Jan 2014 505: 559.
55. Faith JJ. Guruge JL. Charbonneau M et al. The long-term stability of the human gut microbiota. Science. 2013:341, 44-52.
56. Spellerber IF, Fedor PJ. A Tribute to Claude Shannon and a Plead for more Rigorous use Species Richness, Species Diversity and the Shannon-Weiner Index. Global Ecology and Biogeography. 2003 12: 177-179.ithin us. *Molecular Microbiology.* 2006 59(6); 1639-1650.
57. Scott KP, Gratz SW, Sheridan PO, et al. The Influence of Diet on the Gut Microbiota. *Pharmacological Research.* 2013, 69: 52-60.
58. Voreades N, Kozil A and Weir TL. Diet and the development of the human intestinal microbiome. *Frontiers in Microbiology.* September 2014 5 (494).
59. Wu GD, Chen J, Hoffmann C, et al. Linking Long-term Dietary Patterns with Gut Microbial Enterotypes. *Science.* 2011 334(6052): 105-108.
60. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* Jan 2014 505: 559.
61. Faith JJ. Guruge JL. Charbonneau M et al. The long-term stability of the human gut microbiota. *Science.* 2013:341, 44-52.
62. Spellerber IF, Fedor PJ. A Tribute to Claude Shannon and a Plead for more Rigorous use Species Richness, Species Diversity and the Shannon-Weiner Index. *Global Ecology and Biogeography.* 2003 12: 177-179.
63. Varni JW, Sherman SA, Burwinkle TM, Dickinson PE, Dixon P. The PedsQL Family Impact Module: preliminary reliability and validity. Health Qual Life Outcomes. 2004 Sep 27;2:55

13 Attachments

13.1 Table 1: Oral-Motor Skills Required Prior to Starting Protocol

SKILL	Assessment Method	Description	Supports Oral Skill
Age- appropriate strength and coordination of the oral cavity	Observation Manipulation Swallow study (if necessary)	Adequate range of motion, strength and coordinated movement of the lips, tongue, jaw; if safety of swallow is in question, a study will be done to assess	The manipulation of food, either liquid or solid that is appropriate for the child's developmental age or would support adequate nutrition and hydration.
Head/Neck/ Trunk Support	Observation Manual Testing if necessary	Strength and control of the head, neck, and trunk to provide midline stability of the body	Control of the head, neck and trunk support erect posture and alignment so that the mouth is able to manage and manipulate food and there is support surrounding the swallow.
Sensory Processing	Observation, Short Sensory Profile (McIntosh et al., 1999) Interview with family and other care givers	No overt sensory processing issues that interfere with daily life activities, specifically eating/feeding	The ability to organize sensory input supports the mouth's ability to control and manipulate food without reaction to texture, temperature, etc. This in turn supports a safe swallow. Difficulties with sensory processing may set up food aversions that may or may not be directly related to oral skills.

13.2 Table 2: Behavioral Skills Necessary Prior to Week 10 of Protocol

Name of Skill	Descriptor
Regular Meals	Coming to the meal at least 2-3 times per day, willingly.
Limited Grazing	Child does not simply graze throughout the day, but participates in structured family mealtimes.
Same Location	Daily meals take place in the same location.
Meal Length	Meal length falls between 10-20 minutes.
Meal Distractions	There are few distractions during mealtime (ex. TV), that occur on a routine basis. A child who requires distraction in order to take bites is not eligible.
Family Mealtime	The child and family eat meals together on a regular basis.

Structured Start & End	The parent dictates the start and end of the meal with a simple command such as “It’s time to eat” or “You may get down now.”
Parent Behavior During Meals	Parent behavior during meals is appropriate with limited coaxing, never any forcing of food, and no yelling or threatening.
Force Feeding	There is never any forcing of food or other objects into the child’s mouth.
Meal Demeanor	Child is neutral or positive in response to mealtime (voluntarily places food in mouth (or allows adult to do so) without crying, turning head away from spoon.
Good Food Presentation	Appropriate amount/variety of foods are presented in a calm, relaxed manner; feeders announce each bite.

13.3 Table 3. Procedures Timeline

Table 3. Procedures Timeline

Procedures	Pre *(-14 to -1 days)*	Week 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Patient Feeding/Drug Schedule:																										
Tube-feeding via G or G/J			X	X	X	X	X	X	X	X	X															
Tube Taper												X	X													
Megesterol or Placebo												X	X	X	X											
Completed at Each Site:																										
Eligibility	X																									
Informed Consent	X																									
Demographics (REDCap)	X																									
Quality of Life Measures: PIP, ITQOL, PQOL, PedsQL (REDCap)	X											X				X										X
Clinic Visit		X										X				X										X
Vitals (ht, wt, bp, temp, pulse)		X										X				X										X
Blood draw, morning cortisol												X				X										
Stool sample, microbiota		X										X				X										X
Subject Payment ($100)		X										X				X										X
Dispense study drug												X														
Completed by Kansas Team:																										
3-Day Diet Recall	X											X				X										X
Randomization		X																								
Tele-Visit (15-30 min)*			X		X		X		X		X		X	X	X	X	X		X		X		X		X	
Home weight (parent reported)		X	X		X		X		X		X		X	X	X	X	X		X		X		X		X	

*May have additional tele-vistis as needed