1. Title of the Study: Behavioral and Nutrition Treatment to Help Preschoolers with Cystic Fibrosis Grow

2. Date of Submission to CCHMC IRB: 4/11/2005 (vs. 1); 1/25/06 (vs. 2); 1/17/06 (vs. 3); 2/7/06 (vs. 4); 5/15/06 (vs. 5); 7/26/06 (vs. 6); 5/15/07 (vs. 7); 12/12/07 (vs. 8); 2/25/09 (vs. 9); 6/24/09 (vs. 10); 8/25/10 (vs. 11); 9/5/13 (vs. 12)

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5. Abstract: Evidence-based nutritional interventions that achieve and sustain optimal growth in young children with cystic fibrosis (CF) do not exist, despite an urgent need. Such an intervention could positively change the course of clinical lung disease and enhance survival for these children. The objective of this competing continuation study is to conduct a multi-center, randomized, controlled trial comparing a behavioral plus nutrition intervention condition to an attention control intervention condition. All subjects will receive nutritional care consistent with the 2001 CF Consensus Conference guidelines for pediatric nutrition. The specific aims are to: 1. determine the impact of the behavioral intervention on energy intake and weight gain; 2. examine the durability of the behavioral intervention’s impact on growth (weight and height) one year following treatment; and 3. explore the relation between physical activity and growth. The central hypothesis is that behavioral intervention will lead to better growth as measured by change in weight and height for age z scores. From three accredited CF Centers in Ohio (Cincinnati, Columbus, Cleveland), one accredited CF Center in Michigan (Ann Arbor), and one accredited CF Center in Arizona, 100 preschoolers with CF and pancreatic insufficiency age 2 to 6 years will be randomized to one of the two conditions. The two groups will be stratified so that they are similar at the initiation of treatment on weight for age z score. Other critical variables such as history of *Pseudomonas aeruginosa* infection and gender will be used as covariates in the statistical analysis plan. Outcome data (energy intake measured by 7-day diet record, weight, height) will be obtained at baseline, post-treatment (6 months), and after a 12-month follow-up (18 months post baseline). Secondary measures will include body mass index, body composition measured by DXA and skinfolds, and growth velocity. Behavioral treatment will maximize adherence to a high energy diet and enzyme replacement therapy, and motivate children to increase their energy intake. It involves 7 weekly sessions followed by 4 monthly sessions. The attention condition controls for time of contact and number of assessments conducted. This study advances the investigation of early nutritional interventions for young children with CF and directly addresses the need for controlled, longitudinal assessment of behavioral intervention on growth. The long-range goal is to change the standard of nutritional care for young children with CF because behavioral intervention leads to optimal growth and ultimately improves lung health and survival.

6. Key Words: Randomized Clinical Trial, Parent Training, Pediatric Pulmonology, Pediatric Behavioral Medicine, Energy Intake, Child Eating Behavior

7. Purpose of Study: Our long-range goal is to create a behavioral and nutrition intervention that changes the standard of nutritional care for young children with CF because it leads to optimal growth and then test its impact longitudinally on lung health and survival for persons with CF. The objective of this study is to conduct a multicenter, randomized, controlled clinical trial comparing behavioral intervention to an attention control condition. One hundred preschoolers with CF and pancreatic insufficiency age 2 to 6 years will be randomized to one of the two conditions. Our central hypothesis is that behavioral intervention will lead to better growth as measured by change in weight and height for age z scores. We plan to test our central hypothesis and accomplish the objective of this competing continuation application by pursuing the following specific aims:

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Aim 1: *Determine the impact of the behavioral intervention on energy intake and weight gain.*

The behavioral intervention will be compared to an attention condition that allows for control of the number of contacts with the health care team and the number of clinical measurements obtained. All subjects will receive individualized, standard nutritional care based on the consensus recommendation of the U.S. CF Foundation. Our working hypothesis is that the behavioral intervention will produce significantly greater energy intake and change in weight for age z score from pre- to post-treatment (6 months).

Aim 2: *Examine the durability of the behavioral intervention’s impact on growth one year following treatment.*

Our working hypothesis is that greater energy intake and change in weight and height z scores will be found from post-treatment to 12-month follow-up for those children who received the behavioral intervention (12 months).

Exploratory Aim 1: *Examine the relation of physical activity and growth outcomes.*

Changes in weight and height that result from increased energy intake could be affected by a child’s level of physical activity. We will examine this potential confounding variable in two ways. First, in order to attend to the potential impact of physical activity on caloric expenditure, we have based the energy intake goals for the behavioral intervention on normative values for same age/gender children with an active level of physical activity. This benchmark for setting energy intake goals should allow for children in the behavioral intervention to take in more energy than they expend, even if they are quite active, and as a result, show gains in weight and height. Second, because it is possible to obtain data on physical activity using actigraphs in preschoolers, we will include this measure in the clinical trial and examine the relation of physical activity and weight and height outcomes as an exploratory aim. Use of physical activity monitoring in young children is exploratory because the validity of this technology in terms of actual energy expenditure or clinically-relevant levels of activity (such as inactive, light intensity, moderate and vigorous activity) has not yet been demonstrated, and no study has examined this variable in young children with CF.

8. Significance of Study in Relation to Human Health: The proposed research is *innovative* because evidence-based nutritional interventions that achieve and sustain optimal growth in young children with CF do not exist. This next step in our research program will set the stage for tracking the impact of early and effective nutritional treatment on the CF disease process through a child’s life. The *expected outcomes* will address in a controlled, prospective fashion the urgent need to better understand the association between nutritional treatment, growth, and lung function in children with CF and pancreatic insufficiency. We will establish a causal relationship between behavioral treatment leading to energy intake at optimal levels (~ 140% of the age and gender adjusted Dietary Reference Intakes of energy/day for an active physical activity level) that, in turn, results in improved weight gain and growth in young children with CF. This study will provide an evidence base from which to further refine the guidelines for nutritional care of pediatric patients with CF. Our results will have a *positive impact* because families of young children with CF need effective approaches to meet the energy intake goals for this disease and need to know that such approaches lead to improved outcomes. Families of young children with CF and health care providers in CF centers throughout the U.S. need empirical evidence upon which to make nutrition treatment decisions that will lead to optimal growth and long-term health outcomes for children with CF.

9. Previous Work Done in This Area: There is an urgent need for controlled trials of early nutritional interventions for children with CF because of the failure to attain normal growth and nutritional status in this population. The 2003 patient registry of the U.S. CF Foundation (2004) continues to demonstrate that while it is a clear goal of CF care to obtain normal growth, children with CF at all ages do not reach the average weight percentile for age for children in the U.S., and the divergence from the 50th percentile increases with age following a brief period post diagnosis. Farrell et al. (2001) showed in the control condition from a randomized trial of neonatal screening that when children with CF and pancreatic insufficiency are diagnosed in the traditional fashion (near age 2) and receive systematic, individualized nutritional intervention, they obtain an average daily energy intake of 118% of the recommended dietary allowance per day but do not achieve normal growth. There is a lack of evidence-based treatments that lead to energy intake at the CF recommended level of 120 – 150% of the recommended dietary allowance for energy per day (Powers et al., 2003b; Powers et al., 2002; Stark et al., 1995). Furthermore, there is no prospective data from intervention trials demonstrating that improved growth and lung health results from such evidence-based treatments (Konstan et al., 2003; Peterson et al., 2003). For the nutritional care of young children with CF to advance, better interventions must be developed. Our research since the mid-1990’s demonstrates that
such interventions need to incorporate behavioral components that maximize adherence to a high energy diet and enzyme replacement therapy, enhance the delivery of necessary nutrition counseling, and motivate children to increase their energy intake (Powers et al., 2003b; Stark, 2003). The cumulative findings from research over the past decade suggest that for young children with CF and pancreatic insufficiency, optimal growth may only be achieved by energy intake at the upper end of the recommended range and adherence to an effective enzyme replacement therapy regimen (Powers et al., 2003a). The research proposed is significant, therefore, because it advances the investigation of early nutritional interventions for young children with CF and pancreatic insufficiency and directly addresses the need for controlled, longitudinal assessment of the impact of behavioral intervention on growth. By building upon our programmatic clinical research on eating behaviors in young children with CF conducted over the past six years, we are now poised to conduct a multicenter clinical trial that will provide knowledge necessary to help families of young children with CF succeed in meeting the goal of obtaining normal growth. With such knowledge, we can then advance the standard of nutritional care in CF and determine if over time, maintenance of optimal energy intake leads to continued normal growth and long-term preservation of lung health.

10. Research Plan

10.1. Study Sites: This multicenter clinical trial will include three accredited CF Centers in Ohio, one accredited CF Center in Michigan, and one accredited CF Center in Arizona that are also part of the CF Foundation’s Therapeutics Development Center Network (TDN). The sites include Cincinnati Children’s Hospital Medical Center (CCHMC), Nationwide Children’s Hospital (COL), Rainbow Babies and Children’s Hospital in Cleveland (CLE), University of Michigan Health System (UM) and University of Arizona (AZ). The sites have a strong track record of clinical research collaboration within the TDN program. For this trial, collaboration among these centers is crucial to the successful recruitment of an adequate sample to test the study hypotheses. In addition, the multidisciplinary expertise present across these centers affords a unique opportunity to investigate the interactions of behavior, nutrition, growth, and lung health in young children with CF. Cincinnati will be the primary site.

10.2 Design: A prospective, randomized clinical trial comparing behavioral treatment to an attention control condition will be conducted. The control condition was selected because it allows for control of the number of contacts with the healthcare team and the number of clinical measurements obtained. Content for the control condition includes information about the medical care of young child with CF and general anticipatory guidance information for families of young children. All subjects will continue to receive standard nutritional care based on the consensus recommendation of the U.S. CF Foundation. Standard care is individualized based upon a child’s clinical status. The behavioral treatment was developed and pilot tested by the PI during the prior period of R01 funding. Outcomes of energy intake, weight z score, and height z score will be obtained at pre-treatment, post-treatment (6 months), and follow-up (18 months). Secondary outcomes will include Body Mass Index (BMI), body composition (% body fat and lean body mass as measured by DXA and skinfolds), and growth velocity. Additionally, a comparison group will be used to provide data about how young children with CF were responding to “usual clinical care.” De-identified patient registry data will be obtained from the Cystic Fibrosis Foundation to assemble a reference group of children that have received usual clinical care at CF sites that are similar to the ones in the trial on demographics and overall nutritional status of their population. Data on similar aged and gender children will be matched for the trial subjects who meet intent to treat criteria. We will compare height and weight velocity over time between the intent to treat group and the usual care reference group; examine the change in weight and height z score over time between the two groups. Furthermore, we will have a contemporary, data based context in which to interpret the findings of the trial for both the behavioral and attention control conditions.

10.3 Subjects: A total of 100-110 children with CF (age 2.0 to 6.0 years) and their families will be enrolled. Table 1 below shows the feasibility of recruitment of this sample from the 3 original sites (CCHMC, COL, and CLE). Available sample estimates were obtained from each site and represent data for 7/1/05. If we encounter challenges in meeting our goal of 60% recruitment for this clinical trial, a contingency plan has been developed to use the already well established relationships of these 3 TDN centers with nearby CF Centers. For example, Dayton Children’s Medical Center (about 45 miles from Cincinnati) collaborated with the PI on the projects conducted during the prior R01 study and is available if needed to assist with meeting our sample size projections for this clinical trial. It is typical for TDN sites to enroll subjects from nearby centers in clinical research projects. Therefore, we are confident that, if needed, this contingency plan will ensure that a sample of 100 children can be recruited during the planned time line for this trial. Based on recruitment, the University of Michigan CF Center was added as a study site in 7/08.

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To further assist in accelerating our rate of recruitment, the University of Arizona CF Center will begin recruitment in the fall of 2010 as a study site.

**Inclusion criteria:**
1) confirmed diagnosis of cystic fibrosis based upon 2 of the following: a. sweat chloride by quantitative pilocarpine electrophoresis ≥60 mEq/L, b. two clinical features consistent with CF, or c. genetic testing demonstrating two mutations associated with CF
2) confirmation of pancreatic insufficiency based upon fecal elastase of < 100 micrograms per gram of stool (or an undetectable level). This represents a reference value indicative of “severe exocrine pancreatic insufficiency.” Based upon the work of Schall et al. we estimate that 12-20% of children screened will be above this level (Schall et al., 2003).
3) age at enrollment to the trial of 2.0 years to 6.0 years
4) at least 6 months post CF diagnosis
5) consuming an unrestricted fat diet

**Exclusion criteria:**
1) diagnosis of developmental delay (i.e., autism, cerebral palsy, or mental retardation)
2) receiving supplemental enteral nutrition via nasogastric tube, gastrostomy, or total parenteral nutrition
3) diagnosed with another disease/condition (e.g., insulin dependent diabetes, congenital heart disease, significant renal disease, history of bowel resection or short bowel syndrome, colonic strictures) known to affect growth
4) taking a medication (e.g., insulin, growth hormone, chronic use of systemic steroids) known to affect growth
5) screening assessment shows genetic potential for height as acceptable according to the 2001 Consensus Conference guidelines and diet diary indicates daily Dietary Reference Intake (DRI) of energy average of 140% or greater (DRI of 100% will be determined as the estimated energy requirement [EER] based upon the child’s age, gender, and an active physical activity level (Dietary reference intakes for energy, 2002) (Appendix I)
6) weight z score (age and gender adjusted) of > 1.0
7) prior participation in the pilot intervention studies conducted by the PI during the prior period of R01 funding or current participation in an intervention trial conducted by the CF TDN

**Table 1. Feasibility of Recruitment during the first 3 Years of the Study at the 3 Original Study Sites**

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<tbody>
<tr>
<td>Estimated # of eligible subjects at study start date</td>
<td>32</td>
<td>42</td>
<td>25</td>
<td>99</td>
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<tr>
<td>Estimated # of subjects who will become eligible during first 3 years of the study</td>
<td>24</td>
<td>30</td>
<td>15</td>
<td>69</td>
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<tr>
<td>Total number of eligible subjects by end of Year 3</td>
<td>56</td>
<td>72</td>
<td>40</td>
<td>168</td>
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<tr>
<td>Likely enrollees over first 3 years using recruitment rate of 60%</td>
<td>34</td>
<td>42</td>
<td>24</td>
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**10.4 Method of Approach.**

**Step 1. Recruitment.**
Children meeting the inclusion criteria will be identified from the clinical database and/or chart reviews at each CF Center. In accordance with HIPAA policy a waiver for review of the information in the CF Center charts and database will be placed on file with the Division of Health Information Management (or corresponding division at each site) and a file will be kept for patients whose records were reviewed of the study personnel’s access to their medical record for purposes of inviting participation into the study protocol. A letter of invitation and brochure describing the study will be sent to the family from the CF Center director, the child’s primary CF physician, and the principal investigator at each site. A return-addressed, stamped postcard will be included so that families can decline to be contacted further about the study. Families will be instructed to return the post-card if they do not wish to be contacted about the study. Two weeks after the mailing, the families that did not return the post cards will be contacted by phone or in the clinic by the site coordinator to provide further information about the study and inquire about enrolling the child. If the family is interested, an appointment will be scheduled to obtain informed consent and begin the screening assessment. We have utilized this approach to subject recruitment in our prior studies, many across multiple sites, and have found families to be enthusiastic about a project focused on nutrition intervention.
Step 2. Screening Assessment.

Clinical Data from Medical Charts. We will review the child’s records to obtain data regarding their clinical status and clinical care retrospectively for one year prior to the trial and prospectively during the trial. Data collected will include: genotype (currently available for nearly 100% of eligible families at each site); date of diagnosis; history of meconium ileus; weight, height, skinfold measures, and other nutrition status evaluations; enzyme prescriptions, vitamin prescriptions, and prescription of other oral and inhaled therapies; cultures obtained via oropharyngeal methods or bronchoscopy; results from infant pulmonary function testing or other lung function tests; fecal fat testing; bloodwork for vitamin levels; prescription of anti Pseudomonal therapies such as TOBI, CIPRO; pulses of steroid therapy such as prednisone; prescription of Pulmozyme; intravenous antibiotic therapies; hospitalizations. Chart reviews will occur at the beginning of the trial, at 6 months, and after the 12-month follow-up period. These data will be used in determining whether children meet inclusion and exclusion criteria and in describing the clinical characteristics of the participants in this clinical trial. This descriptive information about each child’s medical history during the course of the clinical trial will provide important information in determining limits to the generalizability of the findings.

In addition to the historical inclusion criteria assessed from the database and chart review, the following screening assessments will be conducted:

1) Assessment of pancreatic insufficiency using fecal elastase. Fecal elastase will be evaluated by the Kaleida Heath Women & Children’s Hospital Laboratory (Buffalo, NY). This test requires a small stool specimen (about 1 teaspoon). It has been shown to have outstanding sensitivity and specificity for confirming pancreatic insufficiency in individuals with CF (Cade et al., 2000). Results are obtained within a one week time frame.

2) Determination of weight z score and genetic potential for height. We will categorize weight z score as either $\leq -1.0$ or $>-1.0$ and categorize growth potential as normal (defined as within the 95th confidence interval for the target height; 10 cm for boys and 9 cm for girls) or not at genetic potential. To determine these variables, child weight and height will be obtained at a screening visit using standardized procedures (see description of outcome measures below for details). The heights of the child’s biological parents will also be measured using standardized procedures (or estimated if a parent is not able to be measured). Weight z scores for the child will be calculated using the Centers for Disease Control Anthropometric Software Program (2000 data, Division of Nutrition, Centers for Disease Control, Atlanta, GA). Genetic potential will be calculated by the formulas: (Father’s height – 13 cm) + (Mother’s height) / 2, then adjust by ± 9 cm for girls, and (Mother’s height + 13 cm) + (Father’s height) / 2, then adjust by ± 10 cm for boys (Falkner et al., 1986). The target height and range at age 20 of the gender-specific height-for-age chart is then plotted and used to determine this variable for the child.

Step 3. Primary and Secondary Outcomes Assessment and Plan for Inclusion of Covariates.

Primary Outcome Measures:

Energy Intake will be assessed via 7-day food diaries recorded by parents for children in both groups in this study. For outcome measurement, 7-day food diaries will be collected at pre-treatment, post-treatment, and at follow-up. Accurate measurement of dietary intake is essential to document that behavioral intervention leads to sustained increases in energy intake. Families will be provided with measuring cups, spoons, and an electronic digital Sunbeam food scale. Parents will receive a 60 minute training session to teach them to keep a weighed diet record. They will be provided detailed verbal instructions, modeling and rehearsal with the measurement tools, and written instructions. Information about pancreatic enzymes, vitamins, and other types of nutrient supplement consumption will also be recorded in the food intake records. Identical instructions will be given to both groups by the therapist conducting the initial family session. Research staff will be trained by the PI, Dr. Stark, and Dr. Stallings in how to accurately teach families how to keep a food diary. The treatment manuals for the Behavioral treatment and Attention Control Condition will be used to ensure the same training at each site. We have used this approach to training in our pilot studies with excellent success. Families have completed diet diaries in their homes, taught day care providers and other family members how to complete diaries, and provided detailed and complete records. In over 90% of the measurements obtained in our prior studies, we have been able to collect data for the entire 7 day period. When missing or incomplete records have been encountered, we have used those records for data analysis that have included at least 3 days, of which 2 days were weekdays and 1 day was a weekend day. We did not exclude any data in our pilot study because this 3-day minimum was not met. We will use this plan in the current trial.

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Data from all sites will be analyzed in the General Clinical Research Center at CCHMC using Nutrition Data Systems for Research (NDS-R) software. The NDS-R was developed by the Nutrition Coordinating Center, University of Minnesota (Minneapolis, MN) and is licensed to the GCRC at Cincinnati Children's. It emphasizes standardized data collection and interview techniques, and was designed for dietary research. Default values for unknown information ensure standardized values. The NDS-R has menu driven prompts for complete descriptions of foods and preparation methods. This level of detail is required for research quality calculations of dietary intake of energy, protein, carbohydrates, and fat, as well as micronutrients. The database contains over 18,000 food items (including 8,000 brand name foods), with values for 130 nutrients, ratios, and other food components. The NDS-R is continually updated to reflect changes in the marketplace. There are virtually no missing nutrient values in the NDS-R.

Nutrient data entry and analysis will be performed by an independent diet technician, supervised by the GCRC dietitian. The diet technician will be unaware of child treatment assignment. The diet technician and/or the GCRC dietitian, using the assistance of the therapist as needed, will talk with families to clarify any food entries (this usually occurs by phone). We have successfully used this approach to energy intake analysis in each of the studies conducted during the prior period of R01 support. The average kilocalories consumed per day for a 7-day period and the average percentage DRI for a 7-day period based upon the estimated energy requirement [EER] for the child’s age, gender, and an active physical activity level (Dietary reference intakes for energy, 2002) will be calculated. 

A primary outcome measure for this trial will be average daily energy intake (Aims 1 & 2).

Weight - The child's weight in kilograms will be obtained using a digital Scaletronix scale (Wheaton, IL). Children will be weighed without a diaper (in minimal clothing) and without shoes. Weight to the nearest 100 grams will be taken by a trained research nurse using a standardized procedure based upon the methods described by Lohman et al. (1988). All measurements will be taken in triplicate and the mean used for analyses. To minimize observer bias, the research nurse will be unaware of the subject’s group assignment. The staff at each site will be trained by Dr. Stallings (consultant), an expert in anthropometry in children with CF. [Weight, weight percentile for age, weight z score, and weight velocity will be calculated.] A z-score is a standard score derived from the equation: (actual value - mean value of the population) / standard deviation of the population. The Centers for Disease Control Anthropometric Software Program (2000 data, Division of Nutrition, Centers for Disease Control, Atlanta, GA) will be used to determine z-scores. The 2000 growth charts from the Centers for Disease Control will be used to plot weight. For outcome measurement, weight will be collected at pre-treatment, post-treatment, and at follow-up. 

A primary outcome measure for this trial will be weight for age z score (Aims 1, 2, & Exploratory Aim 1).

Height - The child's height will be obtained using the Holtain stadiometer (Crymych, England). Height will be measured to the nearest millimeter by a trained research nurse using a standardized protocol based upon the methods described by Lohman et al. (1988). All measurements will be taken in triplicate and the mean used for analyses. The stadiometer will be calibrated using a calibration bar prior to measurement at each assessment. To minimize observer bias, the research nurse will be unaware of the subject’s group assignment. The staff at each site will be trained by Dr. Stallings (consultant), an expert in anthropometry in children with CF. [Height in centimeters, height z-score, and height velocity will be reported.] The Centers for Disease Control Anthropometric Software Program (2000 data, Division of Nutrition, Centers for Disease Control, Atlanta, GA) will be used to determine z-scores. The 2000 growth charts from the CDC will be used to plot height. For outcome measurement, height will be collected at pre-treatment, post-treatment, and at follow-up (Appendix E). 

A primary outcome measure for this trial will be height for age z score (Aim 2 & Exploratory Aim 1).

Secondary Measures:

Enzyme Adherence. Adherence with pancreatic enzymes will be assessed via parent report as part of the diet diary recording. Parents will be instructed to record the brand, dosage (number of capsules), and timing (before, during, and/or after) of enzymes given with all meals and snacks on the diet diary record. Adherence will be calculated using the CF INTAKE methodology we developed during the initial period of R01 funding (see below).

Cystic Fibrosis Individualized Nutritional Assessment of Kids Eating (CF INTAKE). This measure evaluates children's adherence to diet and enzyme therapy across five separate categories of behaviors (Powers et al., 2003d; Powers et al., in press 2). The first category examines the number of feedings offered to children (e.g., meals or snacks). The second category measures whether or not children are meeting energy intake goals for each day in the assessment period. The third category measures the adequacy of enzyme use at each feeding. Finally, the fourth and fifth categories examine the types of foods children are eating (e.g., low fat versus high fat) and the use of high fat additives. Data are derived from diet diaries and coded by trained staff. Interrater reliability using Kappa...
coefficients is determined. This new measure has been shown to be reliable and valid for young children with CF. (See Appendix J)

**Body Mass Index (BMI).** Child’s weight and height will be used to determine BMI. The Centers for Disease Control Anthropometric Software Program (2000 data, Division of Nutrition, Centers for Disease Control, Atlanta, GA) will be used to determine BMI z-scores. The 2000 growth charts from the CDC will be used to plot BMI. For outcome measurement, BMI will be determined for each child at pre-treatment, post-treatment, and at follow-up.

**Body Composition: Dual-Energy x-ray absorptiometry (DXA).** DXA using the Hologic QDR 4500A densitometer (DXA; Hologic, Waltham, MA) will be employed to measure total body fat and fat-free mass. This fan-beam densitometer allows for a total body scan in less than 3 minutes. The clinical research centers at each study site have expertise in this technology and the same equipment. Whole body DXA scans will be conducted at baseline and at follow-up. We chose this 18 month interval to allow maximal time for examination of change in body composition, similar to the reasoning for examining linear growth (change in height z score) over this time frame. DXA has been found to be a precise and sensitive measure in pediatric populations. The Cincinnati site has conducted a number of studies involving preschool children and will train and consult with personnel in Columbus, Cleveland, and the University of Michigan to ensure a uniform approach to obtaining these data for the current clinical trial. Cincinnati will serve as the central analysis site for all scans. Estimates of total mass \( r > 0.99 \), percent body fat \( r = 0.97 \), and fat-free mass \( r = 0.99 \) from DXA are significantly correlated with those from the underwater weighing method. The whole body phantom from the GCRC in Cincinnati will be used to calibrate the machines across sites at the beginning of the study. Once calibrated across sites, each site can perform weekly calibration with their own whole body phantom. Quality control is assessed over time by repeat scanning of the phantom. For example, the confidence interval of repeated measurements of a single phantom over a 3.5 month period at the Cincinnati site is 0.4%.

**Body Composition: Skinfold Measurements.** In addition to DXA, skinfold measures at the subscapular, triceps, biceps, and suprailliac sites will be obtained at baseline and follow-up. The staff at each site will be trained in the use of a standard protocol by Dr. Stallings (consultant), an expert in anthropometry in children with CF. Skinfold thickness will be measured on the subject’s right side with a Holtain (Crymych, England) skinfold caliper. Each site has this type of equipment. Measurements will be taken in triplicate at each site and the average will be recorded. Upper arm circumference will be measured with plastic InserTape (Ross Laboratories, Columbus, OH). Body fat will be calculated from the subscapular, triceps, biceps, and suprailliac skinfolds using the prepubertal prediction equations of Brook (1971), which are adjusted for density, body water, and bone density of children. These data will be used in conjunction with the DXA data to determine the child’s body composition. If a DXA scan is not possible for a child due to body movement problems (a possibility for very young preschoolers), the data from the skinfold measurements will be used as the estimate of body fat.

**Parent Questionnaires:** In addition to measuring child outcomes (weight, height, energy intake), we are interested in assessing the impact of the intervention on parents’ experiences and quality of life related to having a child with CF. Four parent questionnaires that are commonly used in CF research (and that we have used in prior studies at CCHMC) have been chosen for our clinical trial project.

The use of self and parent report measures (such as health-related quality of life [HRQOL]) in clinical trials has increased since the Federal Drug Administration strongly recommended their use in 1999. Reasons for including HRQOL measures in trials include: 1.) increased prevalence of chronic diseases has highlighted the importance of assessing how an illness and its treatments affect daily functioning, and 2.) HRQOL provides information with which to compare different treatments. It is important to assess parents’ experiences and HRQOL in this trial, as the increased nutritional needs of children with CF create significant stress for their parents. It is expected that with efficacious intervention parental HRQOL will increase with better nutritional intervention and behavior management skills. Therefore, we would like to include the following measures at baseline, post treatment, and 12-month follow-up. Parents will complete the questionnaires during study visits in which parents will have available time due to the number of outcome measures planned, thus we do not expect that completion of the questionnaires will add a significant amount of time to the protocol. In addition, the questionnaires do not increase risk to the patient or parent.
Cystic Fibrosis Questionnaire: Parent Version (CFQ-Parent Revised). The CFQ-Parent-R is a 44-item parent proxy report of the child’s quality of life (Henry et al. 1997; Quittner et al., 2000). It assesses Physical Functioning, Emotional Functioning, Vitality, School Functioning, Eating Disturbances, Body Image, Treatment Burden, Respiratory Symptoms, Digestive Symptoms, Weight, and Health Perceptions. Raw scores are converted into standardized scores (0-100), with higher scores indicating better quality of life. Internal consistencies coefficients ranged from .58 to .82 for all scales (Quittner, 2005). The CFQ takes approximately 10-15 minutes to complete.

Behavioral Pediatric Feeding Assessment Scale (BPFAS). The BPFAS provides information on mealtime behaviors. It consists of 35 items, with 25 items focused on the child’s behavior during mealtimes and 10 items focused on parents’ feelings about or strategies for dealing with mealtime difficulties. The BPFAS is considered to be a valid and reliable measure for assessing feeding difficulties (Crist, McDonell, Beck, Gillespie, Barrett, & Mathews, 1994). The BPFAS takes approximately 5-10 minutes to complete.

Parenting Stress Index, 3rd Edition. The PSI is designed for the early identification of parenting and family characteristics that fail to promote normal development and functioning in children, children with behavioral and emotional problems, and parents who are at-risk for parenting difficulties. The PSI consists of 120 items and takes about 20 minutes for the parent to complete. This study will use only selected subscales from the measure, which will reduce the items from 120 to 54. It yields a Total Stress Score, plus scale scores for both Child and Parent Characteristics, which pinpoint sources of stress within the family. The PSI is considered a reliable and valid measure of parenting stress (Abidin, 1995).

Family Stress Scale. The FSS is an illness-specific stress measure (Quittner et al., 1990), consisting of 15 items assessing stressors specific to raising a child with CF (e.g., taking medications, doing airway clearance), as well as more common parenting tasks (e.g., behavior problems, following routines). Each item is rated on a 5-point scale ranging from 1 (not at all stressful) to 5 (extremely stressful). Scores are obtained by averaging ratings across items. An internal consistency coefficient of .84 for mothers of children with cystic fibrosis has been reported (Quittner et al., 1992). The FSS takes about 5 minutes to complete.

Pediatric Quality of Life Inventory (PedsQL™, Varni, 1998). The PedsQL™ is a 23-item generic HRQOL measure designed for parents of children and adolescents between 2 and 18 years of age. For the current study, the PedsQL™ Parent Report for Toddlers (ages 2-4) and Young Children (ages 5-7) will be used. The PedsQL™ assesses several domains of functioning, including Physical (8 items), Emotional (5 items), Social (5 items), and School (5 items) and utilizes a 5-point Likert scale (0 = never a problem to 4 = almost always a problem). The PedsQL™ has been found to be valid and reliable for the parent report of a child’s quality of life (r’s = 0.75 to 0.88). This measure takes about 5 minutes to complete.

Plan for Measurement of Covariates and Inclusion of These Variables in the Statistical Analyses:

Determination of history of Pseudomonas aeruginosa (PA) infection. A history of PA infection in early childhood (before age 6) is known to be a major predictor of poorer growth outcomes in later childhood (Emerson et al., 2002). PA infection, relative to other specific pathogens, has the greatest negative impact on prognosis. Therefore, this variable will be used as a covariate representing lung disease status in our statistical analyses. Oropharyngeal (OP) cultures are routinely collected at each study site during clinic visits. In this trial, OP cultures will also be obtained at the baseline, post-treatment, and follow-up study visits. The research nurse at each site will obtain the culture and the analysis will be conducted by a central lab in Cincinnati. Samples will be collected and shipped according to the standard protocol used in prior TDN studies of TOBI in young children with CF. The standard operating procedure used by the TDN is in Appendix F. Staff at each site will be trained to ensure consistency in the technique used to obtain these cultures. The cultures will allow for determination of PA infection, + or -. If a positive PA culture is recorded, we will also track whether it is considered mucoidy. This approach, while not perfect, is consistent with other studies being conducted within the TDN that are tracking infection on the basis of noninvasive assessment techniques. Oropharyngeal cultures are known to show high specificity but are less optimal in terms of sensitivity.
**Gender**: Based on recent epidemiological studies, it is clear that morbidity and mortality related to CF differs between males and females. It is also clear that gender is related to growth over time in children with CF. Thus, this demographic characteristic will be used as a covariate in our statistical analysis plan.

**Physical activity** is another potential confounding variable that could have a negative impact on growth due to increased caloric expenditure or a positive impact on growth due to stimulating growth factors, amongst other effects. It is possible to measure physical activity in children. For example, physical activity can be measured by direct observation, but this approach is costly, time consuming, and impractical in applied clinical research (versus lab observation studies). It can also be measured by self-report questionnaires and diaries; however, this form of measurement has questionable reliability and accuracy. Another approach is to measure physical activity using electric monitors, usually small accelerometer-based activity meters. This approach has recently been utilized in healthy preschool children (Jackson et al., 2003; Montgomery et al., 2004). Both studies used an actigraph monitor (CSA/MTI model 7164; Computer Science Applications, now Manufacturing Technologies Incorporated, Fort Walton Beach, FL) that included a unidirectional accelerometer that measures accelerations in the vertical plane and yields data in the form of counts per minute. The PI has piloted this type of monitor with young children with type 1 diabetes in an ongoing study. While we could find no published studies that have used this technology with preschoolers with CF, it would be possible to obtain data on physical activity using accelerometer-based activity monitors for the preschoolers with CF who participate in this clinical trial. Based on the few prior studies that have involved preschool age children, the assessment method would involve use of a unidirectional actigraph for 3 days, with the measurement interval set at a one minute and the data presented as counts per minute (per valid hour).

Physical activity data measured in this fashion would be exploratory, however, for a number of reasons. First, to our knowledge, no comparable data for preschoolers with CF exist. Second, with the exception of one study that validated activity monitoring in healthy preschoolers with a direct observation measure (Reilly et al., 2003), the validity of these measurements in terms of actual energy expenditure or clinically-relevant levels of activity (such as inactive, light intensity, moderate activity, and vigorous activity) has not been demonstrated. Puyau et al. (2002) explained that based on our current knowledge, it is not possible to precisely predict energy expenditure from measures of physical activity in children at the individual level. Montgomery et al. (2004) further noted that the relation between free-living total energy expenditure and physical activity is unclear for all populations, particularly children. These authors noted a number of practical challenges in determining the relation between caloric expenditure and physical activity, including costs of techniques such as use of doubly labeled water, difficulties in conducting measures of resting energy expenditure in young children, and unresolved issues about how to account for differences in body size. Thus, given the current state of the literature, validated standards upon which to estimate caloric expenditure based on physical activity data obtained from accelerometer-based meters do not exist. As such, the potency of this variable as a covariate is unknown.

Because of the current limitations on interpreting physical activity data in children, especially in preschoolers with CF, we propose to address this potential confounding variable in two ways. First, in order to attend to the potential impact of physical activity on caloric expenditure, we have based the energy intake goals for the behavioral intervention on normative values for children (gender and age specific) with an active level of physical activity. This benchmark for setting energy intake goals should allow for children in this clinical trial to take in more energy than they expend, even if they are quite active, and as a result, show gains in weight. Second, because it is possible to obtain data on physical activity using actigraphs in preschoolers, we will include this measure in the study and examine the relation of physical activity and growth outcomes as an exploratory aim.

**Treatment Modality**: Since the design requires frequent individual visits (namely 8 consecutive weekly visits and 4 consecutive monthly visits), a telehealth (phone) option will be offered to families that endured hardships that made in-person attendance not feasible (e.g. transportation not readily available, lengthy commute, illness in the family). This option requires a family to attend a minimum of 3 of the 8 in-person visits and the remaining visits will be conducted by telehealth. Treatment modality (face to face vs. telehealth) will be used as a covariate in our statistical analysis plan.

**Step 4. Randomization.**

Using the data obtained in the screening assessment, it will be determined if a subject meets all the inclusion criteria and does not meet an exclusion criterion. If eligible, randomization will occur. We will use permuted block size for assignment at each site. Assignment will be qualified so that the two groups are balanced on weight z score. In
this approach to stratification, there will be 2 strata used: weight z score ≤ -1.0 or > -1.0. Assignment will be based upon a predetermined schedule generated by Dr. Bean (biostatistician). Each treatment group will have a total of 50 participants. Planned enrollment in each group is detailed in the Targeted/Planned Enrollment Table.

**Step 5. Begin Treatment Phase.**

**Behavioral Treatment Condition (BEH)** is based on our previous research that shows three primary problems that interfere with optimal energy intake: 1) parents do not typically optimize scheduled meals and snacks and have misunderstandings of enzyme use; 2) parents typically try to attain the CF dietary recommendations by increasing the volume of foods served and consumed instead of increasing the caloric density of foods; and 3) parents’ typical strategies for managing child behaviors at meals are not effective to motivate children to eat consistent with the CF recommendations. Therefore, BEH will combine individualized nutritional counseling that targets increasing energy and fat intake and parent training of effective behavioral child management skills based on social learning theory.

1. *Ensuring appropriate dosage and timing of pancreatic enzyme replacements plus regular meal schedule.*

   Our research on dietary deviations in young children with CF demonstrates that preschoolers with CF are not taking their enzymes consistently and are consistently missing opportunities for meals and snacks. To address this problem, parents in the BEH will be taught to consistently offer 2 snacks and 3 meals each day and to provide prescribed amounts of enzymes at appropriate times (e.g., before meals, not after). Common misperceptions about enzyme dosing such as increased enzyme need means a worsening of disease will be addressed.

2. *Increasing calorie and fat intake, with a goal of meeting the 120-150% DRI for energy, with 40% of calories derived from fat.*

   Our research shows that infants, toddlers, and preschoolers with CF are not meeting the energy and fat intake recommendations for this disease and that parents most often attempt to increase caloric intake by increasing the volume of foods served. However, parents rarely focus on increasing the caloric density of the foods served by identifying high calorie, high fat food substitutes or by adding high calorie addables and spreadables (e.g., butter, cream, sauces). To address this problem, BEH will focus on improving the calorie and fat content of the child’s meals and snacks by using the baseline diet diary to identify changes in specific foods and calorie boosters that will achieve the recommended goals for that child. Parents will be given written general guidelines for increasing calories and individualized booster guides based on their child’s baseline food record. Attention will be given to the food choices recommended, such that the source of the additional calories is considered. For example, dairy products, unsaturated fats, and complex carbohydrates will be incorporated into the individualized recommendations. In our prior studies, we have found that parents of children with CF provide a nutritionally sound diet to their children (Powers et al., in press 1). We have also found that after treatment, this balanced approach to the diet remains (Powers et al., in press 2). Our approach to increasing energy intake and fat intake has been developed over the past 20 years in consultation with a team that included CF physicians, gastroenterologists, endocrinologists, dietitians, nurses, and psychologists. In this trial, collaboration across experts (Drs. Powers, Stark, Stallings, Konstan, and CF dietitians) will be used to ensure that nutritionally adequate and sound decisions are made when recommending ways to increase calorie and fat intake. Micronutrient intake and vitamin and mineral supplementation will also be discussed in the behavioral intervention. Our prior studies have shown that the diet of young children with CF is adequate to meet micronutrient, vitamin, and mineral guidelines (Powers et al., 2003c). In this trial, this important aspect of nutrition in CF will be addressed. Recommendations for dietary changes will be given one meal/snack per intervention session beginning with snack and preceding across breakfast, lunch, and dinner. After intervening to increase the caloric intake at snack and breakfast we have a review session so that children can accommodate to the increased caloric intake at two meals before proceeding to lunch and dinner. Although specific caloric increases are individually based we typically target an increase of 200 calories per day for snack and an increase of 175 calories per day for each meal, with an increase of 600-800 calories per day by the end of the first 5 sessions of treatment. It should be noted that families in the BEH treatment will keep a food record daily throughout the first 2 months of intensive treatment, and one 7-day food record during each month of the maintenance phase of treatment (one session monthly for 4 months).

3. *Teaching effective parent management skills to address common behavioral challenges of toddlers and preschoolers at mealtime.*

   Our research shows that toddlers and preschoolers exhibit challenging mealtime behaviors, that parents of children with CF are engaging in management strategies that are not effective, and parents of children with CF perceive mealtimes as stressful and problematic. For example, young children commonly refuse/reject foods, even those they previously ate. Parents of children with CF respond to these food rejections by coaxing their child to eat or making a game of eating. When these strategies do not work parents offer other foods,
inadvertently becoming “short order cooks.” From a social learning perspective this sequence of behaviors results in increased food rejection because food rejection leads to increased parental attention and changes in food offered. To address these interactional barriers to meeting the CF dietary recommendations, parents will receive training on behavior management strategies at each session focusing on motivating their children to eat foods high in energy and fat. These skills also make the mealtime situation more positive and pleasant. The first skill taught is differential attention. This technique teaches parents to give their attention when their child is engaged in appropriate eating by praising or complimenting the child, describing the behavior (“What a big boy, you took that bite all by yourself. Mommy is proud of you.”) or generally attending and talking to the child when he/she is eating. It also teaches the parent to withhold their attention when the child is engaged in behaviors incompatible with eating. Using the example of food rejection, instead of giving their attention to the child via coaxing the child to eat, parents would be taught to ignore the child when they say they are not going to eat a particular food. However, the parents would also be taught to compliment the child when he/she takes a bite of food, even if it is a different food.

While very effective, differential attention is not always sufficient, especially for behaviors that are impossible to ignore such as leaving the table or throwing food. Therefore, parents will then be taught developmentally appropriate limit setting during meals and snacks to address other problem behaviors that may interfere with consumption of the meal. These skills will include how to give effective commands and set rules and consequences for mealtime behavior. In contrast to usual parenting, behavioral management would help the parents anticipate typical problems and identify appropriate consequences and define these rule and consequences to the child in advance of the meal. As an example, a child would be told that if he/she left the table mommy or daddy would return him/her to the table without talking or that throwing food would result in a brief time out away from the family meal.

Parents will also be taught contingency management. One consistent finding across all our assessment studies is parents of children with CF keep their child at the meal longer than parents of children without CF. We have hypothesized that parents keep their child with CF at the meal longer in hopes that they will eat more. However, we have consistently documented that this is not effective. Therefore we will teach parents to keep meals within the typical 20 minutes found for most children and to motivate the child to eat by providing naturally occurring rewards for appropriate eating either through out the meal or at the end. For younger children this reward may be something as simple as providing a bite or sip of a favorite food or beverage when the child eats a less preferred food. For older children it may include providing access to a favorite video or toy after the meal if the child met their calorie goal. Parents will be taught to end the meal after 20 minutes and not offer food again until the next scheduled meal or snack.

**BEH Treatment Structure.** In this trial BEH treatment will occur over 6 months. During the first 2 months parents will participate in weekly intervention. Intensive weekly treatment will be followed by once monthly treatment over 4 months for maintenance intervention. This approach is based upon the pilot interventions tested during the prior period of R01 funding (Powers, 2003; Powers et al., 2003a; Powers et al., 2004a). The rationale is that weekly intervention involving 5 treatment sessions results in energy intake increases that are over 150% DRI per day. Thereafter, intervention once per month will ensure that children continue this level of intake throughout the remainder of the 6 month treatment. This time line allows for assessment of weight and height outcomes at 2 months (after intensive treatment) and 6 months (after intensive plus maintenance treatment), and monitoring of energy intake weekly for 8 weeks and then one week per month for 4 months. The 4 month period in which a young child has achieved optimal energy intake and maintained that level of intake will allow growth (weight gain) to occur corresponding to the increased energy intake. Therefore, the 6 month time point will be used for our outcome comparison between behavioral treatment and attention control intervention.

<table>
<thead>
<tr>
<th>Week</th>
<th>Session</th>
<th>Topic</th>
<th>Behavioral Child Management Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>How to Keep a Food Record</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Skip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>How to Use Snack to Meet Your Child’s Energy Needs</td>
<td>Differential Attention (compliments, praise and ignoring)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Breakfast: The Most Important Meal of the Day</td>
<td>Contingency Management and Meal Duration</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>Practice Meal: Bring Your Child to Treatment</td>
<td>Refining use of Differential Attention and</td>
</tr>
</tbody>
</table>

Protocol - Behavioral and Nutritional Treatment for Preschool Aged Children with Cystic Fibrosis
Protocol - Behavioral and Nutritional Treatment for Preschool Aged Children with Cystic Fibrosis

Limit Setting

<table>
<thead>
<tr>
<th>Week</th>
<th>Session</th>
<th>Topic</th>
<th>Limit Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>5</td>
<td>Lunch: Consistency Across Situations</td>
<td>How to do it and Do it well</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>Dinner: Making It a Family Effort</td>
<td>Bringing All the Skills Together</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>Review: Putting It All Together &amp; Sick Days</td>
<td>Review and Problem Solve: Making Behavioral Techniques Work for you.</td>
</tr>
</tbody>
</table>

Monthly Booster Sessions (Months 3, 4, 5, & 6)- Parents will attend booster sessions one time each month for four months. A 7-day diet diary will be completed the week prior to the session and data will be reviewed at the meeting. Each session will involve a review of how well calorie intake at each meal is being maintained and the use of behavior management skills with any new mealtime problems. Any decreases in caloric intake will be addressed with specific, individualized suggestions for ways to again meet the calorie intake goals set during intensive treatment. Behavioral management and sick day strategies will also be reviewed at each booster session.

Treatment Integrity: In order to test the efficacy of the behavioral treatment, it is essential that the sessions generally follow the treatment manual guidelines. The principal investigator, along with the other supervising psychologists (Drs. Lemanek and Stark), study coordinator/dietitian (Ms. Chamberlin), and consultant (Dr. Stallings), will train the therapists in the use of the Behavioral Intervention treatment manual and review session videotapes for purposes of ongoing supervision. This approach to staff training has been successful in our prior multisite intervention studies, and ensures that the protocol for behavioral treatment is standardized across sites. An independent evaluator will review 20% of the videotapes for each subject; treatment integrity and accuracy will be judged using session-specific checklists. Sessions will be randomly selected at different time points in the protocol to detect and provide feedback on any therapist “drift.” We will try to prevent therapist “drift” by scheduling regular training reviews (every three months, at the Columbus site). However, if “drift” is identified, the principal investigator will be responsible for therapist retraining.

Behavioral Adherence: Adherence with the behavioral treatment protocol will be examined using the CF INTAKE. When diet records are reviewed at each treatment session, CF INTAKE scores will be determined. If adherence to meal number and schedule, enzyme use, total calorie intake goal, or choices of high energy foods is of concern, the therapist will specifically target those issues during the session.

Attention Control Treatment Condition (ATTN CTL). (See ATTN CTL manual in R01 Grant) In order to control for the amount of contact that families in the BEH condition have with health care providers and to equate the number and timing of outcome measures, an attention control condition was developed for this clinical trial. The curriculum provides families of young children with CF with information about a number of aspects of their child’s CF care and also provides information about typical anticipatory guidance for preschoolers. Informational materials/handouts from the CF Foundation and the American Academy of Pediatrics are incorporated into the curriculum. The intervention was developed with input from clinical care staff at each participating site, and was designed to be meaningful, credible, and enjoyable for participants. While general nutritional information consistent with the Consensus Conference Guidelines is included in the attention control condition, specific techniques that are central components of our behavior and nutrition curriculum (e.g., teaching families to estimate and record calorie intake on the diet records; setting specific, meal-by-meal energy intake goals and providing graphical feedback on progress; integrating behavioral techniques such as shaping with specific energy intake and food choice goals) are not components of the attention control curriculum.

Attention Control Treatment Structure. Just like the BEH intervention, in this trial, Attention Control treatment will occur over 6 months. During the first 2 months parents will participate in weekly intervention. Weekly treatment will be followed by once monthly treatment over 4 months. This time line allows for the same assessments as those obtained for the Behavioral treatment, including weight and height at 2 and 6 months, and monitoring of energy intake weekly for 8 weeks and then one week per month for 4 months. The 6 month time point will be used for our outcome comparison between behavioral treatment and attention control intervention.

Content of the Attention Control Condition Session by Session. (Treatment manual found in R01 Grant)

<table>
<thead>
<tr>
<th>Week</th>
<th>Session</th>
<th>Topic</th>
<th>Informational Handout</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>How to keep a Food Record</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Skip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Enzyme Therapy</td>
<td>None</td>
</tr>
</tbody>
</table>


### Monthly Sessions (Months 3, 4, 5, & 6)

Parents will attend sessions one time each month for four months. A 7-day diet diary will be completed the week prior to the session. These sessions will focus on general anticipatory guidance information for young children, providing families with developmentally relevant health information.

### Specific content for monthly Attention Control Condition sessions is described in the table below:

<table>
<thead>
<tr>
<th>Month</th>
<th>Session</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>8</td>
<td>Social Development (day care, school, sibling rivalry, developmental milestones)</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>Vehicle Safety (things with wheels: cars/car seats, bikes, roller blades, scooters/helmets)</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>Home &amp; Outdoor Safety (burn &amp; injury prevention in kitchen, bathroom; gun safety; pools)</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>Review of CF Care, general health information, and current medical regimen</td>
</tr>
</tbody>
</table>

### Treatment Integrity:

In order to test the efficacy of the behavioral intervention compared to an attention control condition, it is essential that the attention control sessions generally follow the treatment manual guidelines (See Appendix C). The principal investigator, along with the other supervising psychologists (Drs. Lemanek and Stark), study coordinator/dietitian (Ms. Chamberlin), and consultant (Dr. Stallings), will train the study dietitian and nurse at each site in the use of the Attention Control treatment manual and review session videotapes for purposes of ongoing supervision. This approach to staff training has been successful in our prior multisite intervention studies, and ensures that the protocol for treatment is standardized across sites. An independent evaluator will review 20% of the videotapes for each subject; treatment integrity and accuracy will be judged using session-specific checklists. Sessions will be randomly selected at different time points in the protocol to detect and provide feedback on any therapist “drift.” We will try to prevent therapist “drift” by scheduling regular training reviews (every 3 months, at the Columbus site). However, if “drift” is identified, the principal investigator will be responsible for therapist retraining.

### Commonalities for Both Interventions (BEH & ATTN CTL):

All families will receive care from the CF center team at their site based upon the 2001 Consensus Conference Guidelines. These are the clinical care guidelines endorsed by the CF Foundation. Families are seen in clinic at 3 month intervals. Based upon clinical status, more frequent visits and additional care is determined by the CF care team. **Oral Supplements:** In this trial, supplements can be used by both conditions based upon prescriptions that occur as part of standard care. **Enteral Feedings:** If during the trial any child begins enteral feedings (Behavioral treatment or Attention Control), they will continue to receive intervention and their data will be included in the analyses. **Enzyme Therapy and Assessment of Absorption:** As all children will be evaluated by the CF Center team at regularly scheduled clinic visits (every three months) during this trial, our plan for the prescription and adjustment of enzyme replacement therapy will follow the Consensus Conference guidelines for both groups. In our prior treatment studies, we have reviewed gastrointestinal symptoms at each session and reported issues to the CF Center team. The team then worked with the family regarding enzyme prescription and any additional assessments of absorption. Any data regarding enzyme changes or results from absorption tests will be placed in the medical chart and collected during chart reviews conducted as part of this trial. A similar approach to assessing gastrointestinal symptoms and collaborating with the CF Center team will occur in this clinical trial at each Behavioral Treatment and Attention Control Condition session.

### Credibility Measure for Both Interventions:

Subjects in both treatment arms will complete measures of treatment credibility at two time points, one at the end of treatment (6 months) and again at the end of the follow-up period (12 months). The purpose of gathering this information is to document whether or not each of the treatments had similar credibility throughout the trial.

### Subject Retention:

To enhance retention, the design of this clinical trial ensures that all participating families will complete treatment within six months of enrollment. Based upon our prior research, families of toddlers and preschoolers are concerned about the nutritional status and mealtime behaviors of their children. Also, both groups in the clinical trial will receive active and standardized treatments. For these reasons we expect that families will be
interested in completing the project. During treatment we will be flexible in scheduling sessions so as not to disrupt work, day care, or other family activities. Families will receive reimbursement for the time and travel involved in participation. Children will receive gift certificates to a toy store or child clothing store at the end of treatment and after the 12-month follow-up session to acknowledge their efforts. We will send thank you letters to the families and children will receive annual birthday cards from the study team. A biannual newsletter will be sent to inform and update study subjects of study achievements, goals, and news; it will not contain recruitment language. Overall, the intent of the newsletter is to promote study awareness. Any difficulties families have with transportation or the tasks involved in the study will be addressed so that involvement in the project is as easy as possible. In our pilot treatment studies conducted in Cincinnati during the prior period of funding, over 90% of families that enrolled in the protocols finished the study and follow-up. While we expect little attrition, the statistical analysis plan for this clinical trial has allowed for a 16% attrition rate.

**Anticipated Problems:**
1. **Plans to ensure regular attendance at sessions.** It is crucial to the study that the subjects attend their sessions regularly in order to get the full benefit of behavioral treatments. In our experience, subjects are easily engaged in the treatment and enjoy the individual sessions with the therapist. The only challenge we have faced was coordinating schedules with the parents' work schedule. However, we are able to overcome this challenge through flexibility in the therapist's availability on evenings and weekends. As a result, we have had very high levels of attendance and participation (over 95% attendance) in our other treatment studies. Families are reimbursed for their transportation costs for sessions in order to assure their attendance.

2. **Plans for involving parents and other family members, and for addressing day care issues.** As in our prior studies, only one parent or primary caregiver needs to attend the intervention sessions. Of course, the other parent and other family members can attend sessions and often have done so in our pilot studies. If possible, the same family member will attend each treatment session, but we have had success with being flexible such that families can work together to participate in the intervention. For this trial we will work with the primary caregiver to ensure regular attendance at the behavioral intervention or attention control sessions. Of note, the interventions are designed such that the person who attends the intervention sessions learns how to teach other care givers, including day care providers, how to follow the guidelines of the protocol (including collection of diet records, use of skills taught in the behavioral treatment or sharing of the information provided in the attention control condition). We have had success in helping families work with day care providers such that the intervention could be consistently applied for the child throughout the day. We will use the same approach as we did in our pilot studies to ensure that day care issues are actively addressed during the interventions.

3. **Plans to address possible contamination.** Contamination that can occur if families share information about their experiences in treatment is also a potential problem. In recent years, the CF Foundation has made strong recommendations to limit interactions between individuals with CF due to infection related issues. As a result, families of children with CF at the 3 participating sites are recommended to not interact. Even in the clinic, families are separated in the waiting room and quickly taken to treatment rooms to limit exposure to other children. Also, in our pilot studies, we have asked families not to discuss with other families of children with CF the specific content of the intervention. From our experience, this is an effective strategy to limit contamination. We will employ this approach in the current clinical trial to limit the problem of contamination.

4. **Plans to identify and address individual food intolerances.** Information from the child’s medical record and the family will be used to identify food allergies and intolerances prior to initiating treatment. In addition, any concerns that arise during treatment will be brought to the attention of the PI and CF team. We will actively collaborate with the CF team (physician, dietitian) during the course of the treatment to ensure the safe delivery of the intervention.

5. **Plans to recruit families that endure hardships (e.g. transportation not readily available, lengthy commute, illness in the family).** Since the clinical trial requires frequent visits, namely 8 consecutive weekly visits and 4 consecutive monthly visits, we plan to establish a telehealth option which would allow families interested in the study with fewer resources or who live a great distance away from the medical center to benefit from the study. Families would still be required to attend a minimum of 5 sessions at Cincinnati Children’s with their respective therapist. The remaining sessions will be conducted via the telehealth option. We plan to individualize the telehealth option in order to most effectively meet each family’s needs. Treatments sessions will be recorded using a device that will transfer the recorded session directly onto a password protected computer hard drive. Participants will be consented to the recording of the conversation before the session begins. As with the current face-to-face sessions, the treatment sessions must be recorded so they can be rated for treatment integrity.
Step 6. Post Treatment Evaluation
Outcome evaluations will be conducted 6 months after the initiation of treatment, behavioral intervention or attention control condition. These evaluations will include a 7-day food diary to determine energy intake per day, measurement of height and weight, physical activity monitoring, and oropharyngeal culture for P. aeruginosa. The diary will be completed within 2 weeks of obtaining the anthropometric data.

Step 7. Follow-up Evaluation
Families in both groups will receive standard nutritional care provided according to the 2001 Consensus Conference Guidelines during the 12 month period following the interventions. Care is individualized based upon clinical status. Clinic appointments typically occur every 3 months, but may be more often if recommended by the CF care team and/or requested by the family. All care provided will be documented in the child’s medical record. At the end of the follow-up period, outcome evaluations will be conducted. This will be 18 months after the initiation of treatment. These evaluations will include a 7-day food diary to determine energy intake per day and measurement of height and weight. The diary will be completed within 2 weeks of obtaining the anthropometric data. DXA, skinfolds, physical activity, and OP culture for P. aeruginosa will be assessed again at the follow-up. A chart review will be completed at this time to obtain data from the time period of this clinical trial.

Anticipated Problems: It is crucial to the follow-up component of this study that the subjects attend the evaluation visit at 12 months post treatment. In our experience, we have been able to coordinate with family schedules and have had very high level of attendance at follow-up appointments in our prior treatment studies. Families are reimbursed for their transportation costs for the 12-month evaluation visit in order to assure their attendance.

Comparison of Data to De-identified Patient Registry Data from the Cystic Fibrosis Foundation
An application for request for data analyses and access to specific data from the Cystic Fibrosis Foundation Patient Registry will be submitted by Dr. Powers to the CF Foundation Patient Registry Committee. This Data Application and Confidentiality Agreement will be followed to request de-identified patient registry data for age and gender matched children with CF who received standard care in CFF centers across the US during the time of study enrollment. The patient registry will further be matched by identifying CF centers of similar size and population. Patients from all CF centers who enrolled in the clinical trial are excluded (Cincinnati Children’s, Nationwide Children’s of Columbus, Rainbow Babies and Children’s Hospital in Cleveland, two referral sites-Akron Children’s and Dayton Children’s, University of Michigan/Mott Children’s Hospital, and University of Arizona). Matched registry patients must have a confirmed CF diagnosis, be at last 6 months post CF diagnosis, taking pancreatic enzymes, not receiving supplemental enteral nutrition, not diagnosed with CFRD. Registry patients will be selected from encounters from 2006-2010 who are age 2-6 at the time of encounter with both height and weight measured.

Patient registry data will be matched for the trial subjects who meet intent to treat criteria. We will compare height and weight velocity over time between the intent to treat group and the usual care reference group; examine the change in weight and height z score over time between the two groups. Furthermore, we will have a contemporary, data based context in which to interpret the findings of the trial for both the behavioral and attention control conditions. Demographic and diagnosis variables (such as genotype, race, year of diagnosis, method of diagnosis, paternal and maternal height), annualized registry variables (including insurance coverage, socio-economic status, clinic consultations, microbiology results, medications, nutrition, and episodic data on pulmonary exacerbations will also be compared to the intent to treat subjects in the study.

10.5 Statistical Methodology

10.5.1 Power Analysis for Specific Aims 1 and 2: Specific aims 1 and 2 are to determine the impact of the behavioral intervention on energy intake, weight gain, and growth (height gain; Aim 2 only). Power was examined for each of the three endpoints. The procedure for two-group univariate repeated measures ANOVA in the software package nQuery®, version 5.0, was used for the power calculations.

Energy Intake: Data from our most recent pilot study (Powers et al., 2004a) were used to give estimates of calories as a measure of daily energy intake. The means for the behavioral intervention group were 1,314 at baseline, 2,154 at post-treatment, and 1,968 at follow-up. The usual care group did not demonstrate an increase in

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energy intake in the pilot study. However, because families in the planned clinical trial will be receiving an attention control condition, we estimated some increase in calorie intake. Our estimates were 1,399 at baseline (same as in the pilot study usual care group), 1,600 at post-treatment, and 1,600 at follow-up. A standard deviation of 400 was used and the within person correlation was set equal to 0.7. This standard deviation and correlation were determined from a review of data from our prior intervention studies involving children in this age range. For this endpoint, the software yielded a sample size of 39 per group for > 95% power for the interaction, meaning power is ample to detect differences in the rates of the change over the study for the two groups. Power for the group effect is 92%, time effect is > 95%. Two covariates will be used and the correlation among them was set equal to 0.2. Then the factor $1/(1-\rho)$ was calculated and applied to increase the sample size needed. The sample size needed per group is 42. The final sample size of 42 subjects per group allows for an attrition rate of 16%. This is much higher than levels found in our prior intervention trials focused on behavioral treatment to increase energy intake in children with CF, including trials with wait list control conditions. We also examined the minimal difference detectable at follow-up if a t-test were used. With 83% power and $n = 39$ per group, we can detect a difference of 268 calories per day (BEH: 1968 kcal/day minus ATTN CTL: 1700 kcal/day).

**Weight z score:** Estimates of the z-score for weight, at the planned assessment time points for the proposed trial, were obtained from a subset of CF children receiving a behavioral treatment in our largest intervention study for children with CF ($N = 79$). This trial compared weight gain in children receiving a behavioral intervention to a group receiving a nutrition education intervention alone. We followed these children for two years post-treatment. The mean age of the children was 7.5 years with an age range of 4 to 12. Fourteen of the children, in the behavioral arm, were between the ages of 4 to 6 when recruited into the study. The mean z-score for weight was -0.97 at baseline, -0.61 at post-treatment, and -0.46 at 18 months. This mean z-score at baseline is similar to the value found in the most recent pilot study focused on toddlers and preschoolers with CF age 2 to 4 years. For the attention control group, the means at the three points were set equal to -0.97, -0.95, and -0.91. To be conservative, the assumption was made that the control group would show a slight improvement in weight z score over time. The standard deviation was set equal to 0.38 and the within person correlation was assumed to be 0.7. These standard deviation and correlation estimates were determined from a review of the data from our prior intervention studies involving children in this age range. For this endpoint, the software yielded a sample size of 39 per group for > 95% power for the interaction, meaning power is ample to detect differences in the rates of the change over the study for the two groups. Power for the group effect is 92%, time effect is > 95%. Two covariates will be used and the correlation among them was set equal to 0.2. Then the factor $1/(1-\rho)$ was calculated and applied to increase the sample size needed. The sample size needed is 42 per group. The final sample size of 42 subjects per group allows for an attrition rate of 16%. We also examined the minimal difference detectable at follow-up if a t-test were used. With 81% power and $n = 39$ per group, we can detect a difference of 0.25 z score units (BEH: -0.46 minus ATTN CTL: -0.71).

**Height z score:** For this endpoint, time points considered are baseline and follow-up as the expectation is that linear growth is best assessed at an interval greater than 6 months. We again used data from our pilot studies of children in this age range to estimate height z scores. For the behavioral group, the mean z score was -0.5 at baseline and 0.1 at follow-up. The usual care control group had a mean z score of -0.52 at baseline. Again, to be conservative, the assumption was made that the attention control group would show a slight improvement in height z score, to a value of -0.39 at follow-up. The standard deviation was set equal to 0.4 and the within person correlation was assumed to be 0.7. These standard deviation and correlation estimates were determined from a review of the data from our prior intervention studies involving children in this age range. For this endpoint, the software yielded a sample size of 39 per group for > 95% power for the interaction, meaning power is ample to detect differences in the rates of the change over the study for the two groups. Power for the group effect is 85%, time effect is > 95%. Two covariates will be used and the correlation among them was set equal to 0.2. Then the factor $1/(1-\rho)$ was calculated and applied to increase the sample size needed. The sample size needed is 42 per group. The final sample size of 42 subjects per group allows for an attrition rate of 16%. We also examined the minimal difference detectable at follow-up if a t-test were used. With 83% power and $n = 39$ per group, we can detect a difference of 0.27 z score units (BEH: 0.1 minus ATTN CTL: -0.17).

**10.5.2 Sample Size Justification and Feasibility:**
We estimate a total sample available at the initiation of this trial to be 99. During the first three years of this study, we estimate that 69 additional subjects will become eligible. This results in a total sample available by the
end of year 3 of 168. We would need to recruit 60% of these families to meet our sample size goal. In our prior intervention studies we have typically recruited over 75% of eligible families. In our largest intervention study (N=79), we recruited 50% of eligible families across four sites. Therefore, we are confident that 60% of eligible families can be recruited across the three TDN sites participating in this clinical trial. We also have contingency plans with nearby CF Centers who often collaborate on clinical research with these TDN sites. Based upon our track record and the collaboration that has occurred through the TDN across the three sites in this study, we are confident that a sample of 100 families can be recruited into this study over the first 3.5 years. We have also planned for a drop-out rate of 16%, a level much higher than any of our prior intervention studies. Our intention is to recruit and retain a sample of 100 families (50 in each condition). To be conservative, we used 42 in each group for power analysis calculations.

The proposed time line for the study is outlined in the table below. This table reflects the original 3 study sites (Cincinnati, Columbus, and Cleveland) for Years 1-3, and the addition of University of Michigan for Years 4-5 as well as the addition of University of Arizona for Year 5. We will be able to recruit and intervene with families more rapidly if more families are interested than what is outlined in the table.

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Cincinnati</th>
<th>Columbus</th>
<th>Cleveland</th>
<th>Univ of Michigan</th>
<th>Univ of Arizona</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Months 0-4: Study Preparation Months 5-12: Enroll 10 subjects</td>
<td>Months 0-4: Study Preparation Months 5-12: Enroll 12 subjects</td>
<td>Months 0-4: Study Preparation Months 5-12: Enroll 4 subjects</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>Enroll 12 subjects</td>
<td>Enroll 14 subjects</td>
<td>Enroll 8 subjects</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>Enroll 12 subjects</td>
<td>Enroll 14 subjects</td>
<td>Enroll 8 subjects</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>Complete data collection</td>
<td>Enroll 2 subjects</td>
<td>Enroll 4 subjects</td>
<td>Enroll 20 subjects</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>Analyze data; prepare competing renewal to follow the cohort</td>
<td>Complete data collection in first 4 months</td>
<td>Complete data collection in first 4 months</td>
<td>Complete data collection</td>
<td>Enroll 8-10 subjects</td>
</tr>
</tbody>
</table>

* IRB submissions, DSMB collaboration, & development of the manual of operations will take place prior to grant start date pending a fundable score

10.5.3 Data Management:

Dr. Judy Bean, Director of Biostatistics, will work closely with Dr. Scott Powers, Principal Investigator, to provide operational support and consultation for study protocol implementation, data management, and statistical analyses. If the data collected are not of good quality, the analyses are flawed. The goal of the data management plan is to achieve completeness and accuracy of the collected data, while maintaining subject confidentiality. All data for this trial will be sent to the Cincinnati site in hardcopy for data entry and management. Leigh Ann Chamberlin, project coordinator in Cincinnati, will coordinate all communication across the sites regarding data management and will consult with the principal investigator at least twice each week to review this important task. Drs. Powers and Bean will also meet with Ms. Chamberlin and the research assistant in Cincinnati at least once each month to ensure that communication across sites about all aspects of data management and entry are progressing without problems. Dr. Powers will have monthly meetings in person or by phone with research personnel at each site, as well as quarterly in person meetings in Columbus with members of the research teams from all sites. The data management approach will be double data entry, by study personnel, into a SAS database that will be created, using
a combination of SAS/AF and SAS/FSP facilities. The SAS/FSP facility allows customization of data entry and retrieval. The exact image of the form will be copied into SAS and then the data fields will be created. All the edit checking will be contained in the background programming. The advantages to using this SAS based system include ease of data analysis, as the files are already in the correct format, and familiarity of the data entry personnel with this type of system, thus, minimizing data entry error. Customized programs using PROC COMPARE will be constructed to compare the first and second data entry datasets. The data flow of the study will be:

1. When data forms are received, they will log in the data and review them for any errors. If an error is found, upon inspection, a form will be generated that states the error and allows for corrections. The individual making the correction will sign as the adjudicator.
2. The data will be entered into the database by a data entry operator. Skip patterns will be built into the data entry system. All the fields will have range and/or validity checks built into the system.
3. The data will be reentered by the second data entry person, to ensure accuracy. Then two sets of data will be compared and any discrepancies resolved.
4. Data edits will be run to identify missing, out of range, and inconsistent/erroneous data in the database.
5. After the data are entered, more quality control procedures will be implemented using SAS software.
6. The data forms will be kept in a secured cabinet.

The Biostatistics Unit has its own 8–processor Compaq server with over 300 GB usable space, as well as, a Sun server. This server is maintained by the Division of Pediatric Informatics on a 24 hours/day, 7 days/week schedule. Data backups on all servers used by Biostatistics are performed daily with a complete backup being stored in an off campus facility weekly. These tasks are conducted by the Informatics Division of Children’s Hospital. To detect viruses, all email and attachments are scanned routinely using the virus package Inoculan for Windows NT.

On a routine schedule, recruitment reports will be generated and sent to all study personnel electronically.

The de-identified CF Registry Data will be transferred by the CF Foundation to Dr. Powers using a secure server. Data will be stored on a server maintained by the Division of BioMedical Informatics.

10.5.4 Data Analysis:

Steps to be Taken Prior to Conducting the Analyses. The primary statistical package used will be SAS, version 8.2. Prior to any analysis, means, ranges, standard deviations and descriptive measures will be computed for each continuous variable as well as frequencies for categorical variables. If a continuous variable is not normally distributed, a transformation will be performed. All analyses will be done with the transformed values.

Plan for Managing Dropouts. Whenever possible, Dr. Powers will determine from the family the reason for withdrawing from the study. If the family gives consent, minimum data such as height and weight for the individual will be collected at the clinic visit nearest to the time of collection of research variables. These data for the individuals will be used in the analysis. The rate of drop-outs will be determined for each arm of the trial as well and if the rates are not the same, the investigators will explore the reasons for this. In prior studies, no differential rate occurred in the groups.

Intention-to Treat Analysis Plan, Per Protocol Analysis Plan, and Plan for Addressing Missing Data. The primary approach to the analysis is intention-to-treat and not per protocol analysis. The subject will be considered evaluable for response if they attend at least one behavioral or attention control session. For the per protocol analysis, the population will consist of all subjects who attended ≥ 80% of the intervention sessions and completed at least the baseline and post-treatment assessments. Although every effort will be made not to have missing data points and not to have drop-outs, these may occur. To ascertain if the missing data have an impact upon the inferences to be made from the trial, different analyses will be performed. If the missing variable (such as weight and height) can be obtained from the nearest clinic visit it will be used in all the analyses. The first approach will be to estimate the missing data points. Due to bias, the method of last value carried forward will not be used (Little et al., 1996). First, energy intake, weight for age z score, height for age z score (and values for secondary measures) will be estimated using the approach of regression in Solas®. This imputation method may be best as the predicator variables are expected to have a strong relationship with the primary outcomes measures in this investigation. If examination of the data does not reflect this strong relationship, other imputation methods will be chosen. It is possible that for certain variables, regression will be the preferable method whereas, for others, group means may be better. Then the dataset consisting of the observed data plus the estimated values will be used in the analyses. In every analysis...
where missing data is an issue, the percentage of missingness as well as the extent to which the missingness is ‘random’ will be evaluated. There are several levels of randomness to pay attention to, and researchers have advised against the use of missing data imputation in instances where missingness is correlated with the main dependent variables of the study (Rubin, 1987). Another analysis will use only the observed data in modeling and finally only the completed cases will be modeled. These different approaches to the missing data problem will permit an examination of the impact of the missing information upon the results. When reporting the results, the assumptions made for each of these different approaches will be indicated.

**Plan for Addressing the Issue of Compliance.** Another issue is compliance. In this type of behavioral therapy investigation, no good measures of compliance such as pill count or serum levels exist. Data will be recorded for each family as to whether or not they attend each session. The rate of compliance in the two groups will be compared. Weighting by these proportions will be considered if the rates are different.

**Plan for Conducting Univariate Analyses.** The groups will be compared to ensure that randomization worked. The demographic characteristics such as age will be compared. For continuous variables, a two-sample t-test will be used and for categorical variables chi square tests. The covariates will be examined to determine if they differ in the two groups. Regardless of the outcome, history of Pseudomonas aeruginosa infection, gender, and treatment modality will be covariates in the analysis. Correlation coefficients among various variables such as change in weight for age z score and change in energy intake will be calculated. The analysis will indicate if the difference seen in weight for age z score is partially explained by an increase in energy intake.

**Plan for Conducting Longitudinal Analyses.** We will formally examine change from pretest to 6 month posttest (for energy intake and weight-for-age z) and pretest to 18 month follow-up (for height-for-age z) via analysis of covariance models with the following pre-specified covariates: gender, Pseudomonas status, treatment modality, and the pretest measure for the respective outcome. The outcome for a given analysis will depend on the particular hypothesis of interest. If missing data are present, we will employ a repeated measures model, analogous to analysis of covariance, with maximum likelihood (ML) estimation using PROC MIXED to estimate the treatment effect of interest, \[ y_{it} = \beta_0 + \beta_1 Time_t + \beta_2 Grp \times Time_t + e_{it}, \] where \( y_{it} \) is the outcome variable at time \( t \), \( Time_t \) is coded 0 for pretest and 1 for posttest or follow-up, \( Grp \) corresponds to either the BEH or ATTN CTL group, and the primary effect of interest is \( \beta_2 \), which corresponds to the group difference on change in the outcome of interest from the pretest to the posttest or follow-up. The ML estimation approach is valid when missing data are missing at random, and will be useful for examining the sensitivity of our effects to missing data.

**Plan for Analysis of Secondary Measures.** Exploratory analyses will be performed for BMI, DXA percent fat, and DXA percent lean mass. First, simple univariate comparison will be done between the two groups. Then modeling will be performed. The model will follow the template given above.

**Use of Growth Velocity (a secondary measure) to Examine the Clinical Significance of the Findings.** As noted, growth velocity is an extremely important variable regarding how the child is doing clinically in terms of meeting the goal of normal growth. To examine clinical significance, weight and height velocity for the two groups will be compared at six months and then again at 12 months. As we have done in our pilot studies, we will use a clinical benchmark of weight and height velocity at or above the expected growth for a same age and gender child who is healthy and following the 50th percentile trajectory. In the age range of 2-6 years, these benchmarks are 1.0 kg per 6 months and 3.5 to 4.5 cm per 6 months. In this trial, the proportion in each group from baseline to six months that meets the benchmark will be computed. This proportion will also be calculated for each group from post-treatment to twelve month follow-up (12 months). At each time point, six and twelve months, a chi-square test will be performed. With 42 per group, a chi-square test with a .05 two-sided significance level will have 86% power to detect the difference between the behavioral group with 70% reaching the benchmark and the attention control group having 35% reaching the benchmark.

**Plan for Physical Activity Data Analysis (Exploratory Aim 1).** The relation of physical activity and growth outcomes will be explored. Based upon actigraph measurement of physical activity, counts per minute over 3 days taken at the three points, baseline, post treatment, and follow-up, will be recorded. First, we will examine whether there are differences between the groups at baseline. Next, we will examine if physical activity changes across time and if there is a differential effect of the interventions on this variable (time x group interaction). Finally, if differences are not found between groups or over time, we will examine the correlation of physical activity and the study endpoints in the following fashion: a. the average of baseline and post treatment data will be computed as well
as the average of post treatment and follow-up data. Combining two 3-day measurements will be done to provide a better estimate of a child’s activity than a single data point. b. The average counts per minute at baseline and post-treatment will be correlated with the change in energy intake, weight z score, and height z score from baseline to post-treatment. c. The average counts per minute at post-treatment and follow-up will be correlated with the change in energy intake, weight z score, and height z score from post-treatment to follow-up. Pearson product-moment correlations will be used. Based upon these analyses, we will better understand how the two groups compare on physical activity and how this variable relates to the study endpoints. If physical activity differs at baseline between the groups, or if a time effect or a time x group interaction effect is found, an exploratory model including physical activity will be examined to see if this variable explains any of the observed variability in the growth outcomes. With a sample of 42 in each group and a correlation of 0.2 among the covariates, a model that includes 3 covariates (Pseudomonas infection, gender, and physical activity) would have > 90% power for the interaction.

11. List of other previously approved research studies in which the projected patient population may also be involved: None.

12. Components of CCHMC that will be utilized: CF Center/Pulmonary Medicine, Division of Psychology, General Clinical Research Center

13. Special Considerations:

13.1 Radiation Safety: Application has been submitted to Sara O’Hara, MD, CCHMC Radiation Safety Committee because of the use of DXA. The DXA measurements carry the risk associated with radiation exposure, but the radiation exposure is very small and well below the limits set for research in pediatric subjects of 1000 μSv a year. The radiation exposure (effective dose) associated with the whole body DXA scan at each visit is 4 to 5 μSv. The total radiation exposure for participating in the study (2 whole-body measurements) is 8 to 10 μSv, which is equivalent to approximately ≤ 1 day of background radiation exposure. There is no benefit from this extra radiation exposure.

13.2 No other special considerations applicable

14. Potential Benefits: The knowledge gained in this study has the potential to identify an efficacious treatment to improve growth in toddlers and preschoolers with CF and pancreatic insufficiency. Both groups examined in this study will receive regular care based upon the current consensus for standard care. Half of the families will also receive behavioral treatment and half will receive an attention control intervention. Both interventions contain information that is relevant to the care of a young child with CF. The results could lead to more efficacious clinical interventions to improve energy intake and growth for this population. Children participating in this study will receive the most current information on nutritional care for CF.

15. Potential Risks, Discomforts, Inconveniences, and Precautions: Some data will be obtained directly from the children and their parents in the current study. These data include demographic and general health information, weight, height, energy intake by diet diary, oropharyngeal cultures to determine presence of Pseudomonas infection, physical activity monitoring by actigraph and log, and chart review to document nutritional treatment and other aspects of CF clinical care. In addition, body composition will be measured by skinfold measurements and dual-energy x-ray absorptiometry (DXA). Fecal elastase tests to document pancreatic insufficiency will be conducted. In our prior studies, minimal risk has been associated with the interventions and assessments. In terms of risks and discomforts in the current study, we discuss the minimal radiation exposure from the 2 DXA assessments and our plans for data and safety monitoring below:

**DXA Assessments.** The DXA measurements carry the risk associated with radiation exposure, but the radiation exposure is very small and well below the limits set for research in pediatric subjects of 1000 μSv a year. The radiation exposure (effective dose) associated with the whole body DXA scan at each visit is 4 to 5 μSv. The total
radiation exposure for participating in the study (2 whole-body measurements) is 8 to 10 µSv, which is equivalent to approximately ≤ 1 day of background radiation exposure. There is no benefit from this extra radiation exposure.

**Data and Safety Monitoring Plan.** This study is a Phase III clinical trial with children. Therefore, we recognize the need for a careful data and safety monitoring plan to ensure the well-being of the children in this study and the scientific integrity of the project. We are proposing that a data safety monitoring board (DSMB) be appointed by NIDDK to provide regular oversight of data and safety monitoring issues as detailed in the document "NIDDK Data and Safety Monitoring Guidelines for Clinical Trials." These experts will periodically review and evaluate the accumulated data for participant safety, adverse events, study conduct and progress. The DSMB will make recommendations to the appropriate regulatory agencies (IRB, NIDDK) concerning continuation, modification or termination of the study. A Manual of Operations will be developed for this clinical trial and approved by the DSMB. If found to be the best approach by the NIDDK, the DSMB of the Cystic Fibrosis Foundation (a group that provides independent oversight of TDN studies as well as some NIH-funded clinical trials in collaboration with NIDDK) will be asked to consider serving this critical function for the proposed clinical trial. Dr. Bonnie Ramsey, Director of the TDN coordination center, is supportive of this request of the CFF DSMB. Dr. Wayne Morgan, Chair of the CFF DSMB, is also supportive of serving as the DSMB for this clinical trial. We are proposing that the DSMB have one face-to-face meeting at the beginning of the study (followed by yearly phone conference meetings). In addition, provision should be made for an emergency meeting should any serious adverse events occur in the interim. We have budgeted for this plan. The principal investigator and the biostatistician on the study will jointly prepare regular reports for the DSMB to review at each meeting. The reports will include a summary of the following topics:

**Performance monitoring:** A report of subject recruitment, comparison with targeted recruitment, retention, protocol adherence and quality of data collection procedures.

**Safety Monitoring:** A review of safety of the subjects, including confidentiality, any adverse events or side effects related to the treatment (in a blinded fashion).

**Treatment Monitoring:** The committee will be provided data on treatment integrity and compliance. This will include the data from the personnel who will be reviewing videotapes for behavioral intervention and attention control intervention sessions randomly selected at different time points in the treatment. In addition, we anticipate having sufficient data on the treatment groups by the end of Year 3 (approximately 15-20 subjects per group), for the study biostatistician to generate preliminary data on efficacy for the committee to review.

**Stopping Rules:** If a serious adverse event as a result of participation in the study occurs, subject accrual will discontinue until the DSMB has reviewed the information and the subject has received adequate care. Subject recruitment will commence again only after the DSMB has given the investigators the permission to continue. In addition, if the subjects in the behavioral treatment arm are not showing beneficial response to treatment (i.e. no significant change in growth) then the committee may make a determination that the study be modified or the trial be discontinued. Finally, if during the course of the trial new information becomes available about the effects of behavioral intervention or other major advances in nutritional care for young children with CF that significantly impacts treatment approaches, then the DSMB may review the evidence to make a decision about discontinuing the trial.

Since patients will continue to be monitored during their participation in this study, the need for additional medical interventions should be readily identified. During this study, parents may express or experience concerns or stress related to parenting a young child with CF and issues related the child’s health (e.g., weight change, pulmonary exacerbations). If this occurs, families will be provided assistance from a trained professional who is not involved in the clinical trial. As part of standard practice at each participating CF Center, a social worker is an active member of the multidisciplinary team. These trained professionals will be available to families who participate in this clinical trial to discuss feelings and stresses related to parenting a young child with CF. This assistance will be specifically offered to families when they are enrolled in the study.

*Based upon the information in this protocol, we recommend that the proposal be classified as minimal risk, with potential direct benefit to participants.*

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16. Confidentiality: All participating patients will receive an identifying number for coding and analyzing data. Data obtained as part of the patients’ participation in this study will be stored in a secure location at the site coordinators office and a duplicate copy will be kept by the project PI, Dr. Powers, in a secure location in his research office in Cincinnati.

17. Period of Time Estimated to Complete Project: 5 years (2005-2010)

18. Funding: NIH/NIDDK Grant # 2 R01 DK054915-06A1 (PI: Scott W. Powers)

19. Payment for Studies: We plan to reimburse families for their travel, parking and time for the assessment sessions, intervention sessions and a follow-up session (for collection of data). Many families seen at our hospital travel over 30 minutes to reach the medical center. Few could afford the gasoline, parking, and meals that are required for extra visits for participation in this study. Families in this study will also be asked to keep a seven-day food record which requires a great deal of time and effort. Payments to families are itemized across the following categories:

   1. Evaluations. Each family will participate in a pretreatment, post treatment, and follow-up evaluation. For a pretreatment evaluation, the families will receive $20 to compensate for their travel expenses and $50 for the time involved in collecting the diet diaries. At the post treatment assessment, families will receive $20 for their travel costs, $50 for completion of the diet diary, and the young child will receive a $20 gift certificate to a toy store or child clothing store to recognize their successful completion of the first phase of the study. For the follow-up evaluation, families will again receive $20 for travel, $50 for completing the diary, and the child will receive a similar $20 gift certificate. Therefore, the pretreatment evaluation reimbursement is $70, the post treatment and follow-up assessment reimbursements are $90.

   2. Families will be compensated for each treatment session (behavioral or attention control) that they attend. This will involve a total of eight sessions not counting the evaluation visits. Families will receive $30 compensation for their time and travel costs related to each of these visits. This equals a total of $240 for each subject.

20. Method to be used in procuring consent of subjects: Participants for this study will be identified by the research coordinator and CF physician at each site. In accordance with HIPAA policy a waiver for review of the information in the CF Center charts and database will be placed on file with the Division of Health Information Management or corresponding division at each site and a file will be kept for patients whose records were reviewed of the study personnel’s access to their medical record for purposes of inviting participation into the study protocol. Letters will be sent to eligible families from the CF Center Director, primary CF physician, and the principal investigator at each site. This letter will include a brochure describing the study and identifying the principal investigator and research staff and invite them to participate. A return-addressed, stamped postcard will be included so that families can decline to be contacted further about the study. Families will be instructed to return the postcard if they do not wish to be contacted about the study. Within 10 days of mailing the letter, families who do not return a postcard will be contacted by phone by the project coordinator and/or research assistants to invite the family to participate in the study. If a family agrees they will come to the CF Center to conduct a formal consent process and then begin screening assessments. Families will be explicitly told that their medical care at their CF Center will not be affected whether they choose to participate in the study or to decline participation. At this initial study visit, the research coordinator will assist the family in reviewing the consent form. If the family agrees to participate, the parent will sign the consent and screening assessments will begin.

21. Permission of patient’s attending CF physician: We will obtain permission from the CF Center team prior to contacting any potential participants. Dr. Gary McPhail, co-investigator, will coordinate this with the PI.

22. Inclusion of Women and Minorities. We expect to have an equal balance of male and female subjects. Since CF overwhelmingly affects Caucasians, we expect to most subjects will be white. We will recruit minority individuals if they are patients at the respective centers.
Data regarding the gender and race/ethnicity of eligible subjects at each of the 4 participating sites is found in the table below:

<table>
<thead>
<tr>
<th></th>
<th>Cincinnati</th>
<th>Columbus</th>
<th>Cleveland</th>
<th>UM</th>
<th>AZ</th>
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<tbody>
<tr>
<td>Gender (Male/Female)</td>
<td>13/19</td>
<td>15/17</td>
<td>10/6</td>
<td>13/7</td>
<td>4/4</td>
</tr>
<tr>
<td>Race (Caucasian/Other)</td>
<td>32/0</td>
<td>32/0</td>
<td>16/0</td>
<td>20/0</td>
<td>8/0</td>
</tr>
<tr>
<td>Ethnicity (Non-Hispanic/Hispanic)</td>
<td>32/0</td>
<td>32/0</td>
<td>16/0</td>
<td>20/0</td>
<td>8/0</td>
</tr>
</tbody>
</table>

23. Inclusion of Children.

Children ages 2 to 6 years will be the subjects for this project as we are focusing on improving energy intake and growth in toddlers and preschoolers with CF and pancreatic insufficiency.

24. References.


Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (Macronutrients). (2002). In *Dietary Reference Intakes* (pp. 93-206; Energy).


Summary of Protocol Revisions

**Version 2 (1/25/2006)**
Based on current literature and clinical practice, the fecal elastase inclusion criterion used to confirm pancreatic insufficiency was modified from ≤ 15 micrograms per gram of stool to < 100 micrograms per gram of stool. This represented a reference value indicative of "severe exocrine pancreatic insufficiency."

**Version 3 (1/27/2006)**
Two parent handouts were added to provide parents with an overview of two study procedures (DXA and fecal elastase test). Four parent questionnaires commonly used in CF research [Cystic Fibrosis Questionnaire: Parent Version (CFQ-parent Revised); Behavioral Pediatric Feeding Assessment Scale (BPFAS); Parenting Stress Index, 3rd Edition (PSI); Family Stress Scale (FSS)] were also added to assess the impact of the intervention on the parent’s experiences and quality of life.

Clarification was provided stating that only selected subscales on the Parent Stress Index (PSI) were to be administered, reducing the number of items from 120 to 54. In addition, the Pediatric Quality of Life Inventory (PedsQL™), a 23 item questionnaire, was added to assess domains of functioning (physical, emotional, social, and school).

A Release of Information Form to be signed by the participant’s parent or legal guardian was added to grant study personnel permission to contact the participant’s school or daycare to obtain dietary intake information.

**Version 6 (8/18/2006)**
An adjustment in the provision of treatment sessions was made to provide an opportunity for families that endure hardships (e.g. transportation not readily available, lengthy commute, illness in the family) to participate in the trial using a telehealth option for some of the study visits.

**Version 7 (5/25/2007)**
Change in site investigator was made at Cincinnati Children’s.

**Version 8 (1212/2007)**
An affiliated study site’s legal name was changed from Columbus Children’s Hospital to Nationwide Children’s Hospital

The University of Michigan was added as an additional study.

**Version 10 (7/18/2009)**
A biannual newsletter was added to provide participant’s families with an update on study achievements, and promote study awareness.

**Version 11 (9/29/2010)**
The University of Arizona was added as a study site to further accelerate the rate of recruitment. The planned number of recruited subjects was increased from 100 to 110 to allow for screen fails or participants who did not complete the full protocol.
The study design was modified to examine a height and weight among a comparison group to provide data about how young children with CF were responding to “usual clinical care.” The comparison group was comprised of de-identified patient registry data obtained from the Cystic Fibrosis Foundation.