Effect of Elemental Diet on Adult Patients with Eosinophilic Gastroenteritis (ELEMENT)

Protocol Date: 09/10/2019

NCT03320369

Rare Diseases Clinical Research Network (RDCRN)

Effect of Elemental Diet on Adult Patients with Eosinophilic Gastroenteritis (ELEMENT)

Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)

This protocol is for research purposes only, and should not be copied, redistributed or used for any other purpose. The procedures in this protocol are intended only for use by Consortium investigators in carefully controlled settings. The Chair of this study should be consulted before using or attempting any procedure in this protocol.

Nirmala Gonsalves, MD
n-gonsalves@northwestern.edu

Version 3.0
10Sep2019

INVESTIGATOR SIGNATURE PAGE	
Protocol: CEGIR 7809	**Version/Date:** Version 3.0; September 10, 2019
Site Principal Investigator:	
Title: Effect of Elemental Diet on Adult Patients with Eosinophilic Gastroenteritis	
Study Sponsors: National Institute of Allergy and Infectious Diseases (NIAID) Division of Allergy, Immunology and Transplantation (DAIT) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Office of Rare Diseases Research (ORDR) National Center for Advancing Translational Sciences (NCATS)	
INSTRUCTIONS: *The site Principal Investigator should print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent. After signature, please upload the signed document to the DMCC E-regulatory binder.* Jessi Lipscomb, Research Project Manager Data Management and Coordinating Center (DMCC) Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Suite 455AC Cincinnati, Ohio 45229	
I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements. As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID. **Confidentiality Statement** This document contains confidential information of the Sponsor. This information is to be disclosed only to the recipient study staff and the Institutional Review Board or Board of Ethics Committee reviewing this protocol. This information can be used for no other purpose than evaluation or conduct of this study without prior written consent from the Sponsor _____ **Site Principal Investigator (Print)** _____ **Site Principal Investigator (Signature)** **Date**	

KEY ROLES

Protocol Chair: Nirmala Gonsalves, MD

Institution: Northwestern University
Address: 676 North Saint Clair, Suite 1400, Chicago, IL 60611
Phone: 312-695-5620
Fax: 312-695-3999
Email: n-gonsalves@northwestern.edu

NIAID Medical Monitor: Amanda Rudman Spergel, MD

Institution: Division of Allergy, Immunology, and Transplantation – NIAID/NIH
Address: 5601 Fishers Lane, Rm 6B54
Bethesda, MD 20892
Phone: 240-627-3840
Fax: 301-480-4258
Email: rudmana@niaid.nih.gov

NIAID Project Manager: Katherine Thompson, RNP, MSN, CCRP

Institution: Division of Allergy, Immunology, and Transplantation – NIAID/NIH
Address: P.O. Box 7
Lecanto, FL 34460
Phone: 301-760-1177
Email: Thompsonkath@niaid.nih.gov

Data Management and Coordinating Center Principal Investigator: Eileen King, PhD,, PhD

Institution: Cincinnati Children's Hospital Medical Center
Address: 3333 Burnet Avenue, Suite 376
Cincinnati, Ohio 45229
Phone: 513-803-1819
Email: Eileen.King@cchmc.org

Data Management and Coordinating Center Principal Investigator: Peter White, PhD

Institution: Cincinnati Children's Hospital Medical Center
Address: 3333 Burnet Avenue, Suite 443
Cincinnati, Ohio 45229
Phone: 513-803-4172
Email: Peter.White@cchmc.org

Data Management and Coordinating Center Principal Investigator: Maurizio Macaluso, MD, DrPH

Institution: Cincinnati Children's Hospital Medical Center
Address: 3333 Burnet Avenue, Suite 272
Cincinnati, Ohio 45229
Phone: 513-636-2710
Email: Maurizio.Macaluso@cchmc.org

Protocol Synopsis

Title	Effect of Elemental Diet on Adult Patients with Eosinophilic Gastroenteritis (ELEMENT)
Clinical Phase	Pilot
IND Sponsor/Number	Marc Rothenberg / 13Jul16 Notification of exemption
Study Objectives	To prospectively evaluate the clinical effectiveness of a food allergen-free diet consisting of elemental formula in controlling histologic eosinophilia in adults with eosinophilic gastritis/gastroenteritis.
Study Design	Pilot study of individuals age 18 to 65 yrs with EG/EGE
Primary Endpoint(s)	Improvement in eosinophilic inflammation as determined by percent of patients who have achieved complete histologic remission. Complete histologic remission will be defined as normalization of mucosal eosinophilia (histology with less than the diagnostic threshold levels of mucosal eosinophilia (<30 eos/HPF))

Secondary Endpoint(s)	Secondary endpoints will be mean percent change in eosinophil density defined as (baseline absolute peak eosinophil density - final absolute peak eosinophil density)/baseline absolute peak eosinophil density; and percentage of patients who have had partial histologic remission defined as a 50% reduction in baseline mucosal eosinophilia. Exploratory outcomes include improvement in symptoms, endoscopic features, peripheral eosinophilia, and quality of life scores. We will utilize validated patient reported outcome instruments.
Accrual Objective	25 subjects
Study Duration	Individual duration is 8 weeks; Participants have the option to allow prospective data collection up to a year from the time they complete the diet portion of the study.
Treatment Description	Elemental formula every day by mouth for 6 weeks
Inclusion Criteria	1. Participant must be able to understand and provide informed consent 2. Males and Females ≥18 to 65 years of age; 3. Have diagnosis of EG/EGE 4. Have histologically confirmed active disease ≥ 30 eosinophils/hpf 5. Symptomatic (have experienced symptoms within the last one months prior to enrollment). 6. Female subjects of childbearing potential must have a negative pregnancy test upon study entry 7. Female (and male) subjects with reproductive potential, must agree

	to use FDA approved methods of birth control for the duration of the study
Exclusion Criteria	1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol 2. Secondary causes of gastrointestinal and peripheral eosinophilia 3. Eosinophilic infiltration isolated to the esophagus. 4. Pregnancy 5. Immunodeficiency states 6. Have been treated with topical swallowed steroids within the last 6 weeks or systemic steroids within the last 2 months unless repeat endoscopy is performed and shows active inflammation on these therapies in which case these medications will be allowed to be continued without dose escalation. 7. Have taken immunosuppression medication or immunomodulators within 2 months of the study unless the recent/baseline endoscopy has active histologic inflammation while on these medications. In this case, these medications will be permitted to be continued as long as dose is not escalated during the treatment phase. 8. Have been on an elemental diet previously for six weeks with follow up endoscopy completed. 9. Have participated in any investigative drug study within 6 weeks prior to study entry. 10. Unable to complete study procedures including endoscopy. 11. Hyponatremia 12. At risk for fluid or electrolyte imbalances during the study (e.g. on high dose or multiple diuretics, clinically significant renal insufficiency (decreased GFR), unusually high or low fluid volume intake that could result in electrolyte abnormalities) 13. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.

Study Stopping Rules	1. Investigator or sponsor request to withdraw from study participation. 2. Serious and/or persistent noncompliance by the investigator with the protocol or other local applicable regulatory guidelines in conducting the study. 3. IRB decision to terminate or suspend approval for the investigation or the investigator.

Table of Contents

Glossary of Abbreviations

AE	Adverse Event/Adverse Experience
CBC	Complete Blood Count
CEGIR	Consortium of Eosinophilic Gastrointestinal Disease Researchers
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DMCC	Data Management and Coordinating Center
DSMB	Data Safety Monitoring Board
EC	Eosinophilic Colitis
ED	Elimination Diet
EG	Eosinophilic gastritis
EGE	Eosinophilic gastroenteritis
EGID	Eosinophilic Gastrointestinal Disease
EoE	Eosinophilic esophagitis
Eos	Eosinophils
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HPF	High Power Field
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Personal Health Information
PI	[Site] Principal Investigator

PROMIS	Patient Reported Outcome Measurement Information Systems
QA	Quality Assurance
RDCRN	Rare Diseases Clinical Research Network
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SFED	Six Food Elimination Diet
SMC	Safety Monitoring Committee
SMS	Specimen Management System
SOC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction

1. Background and Rationale

1.1. Background and Scientific Rationale

Eosinophilic gastrointestinal disorders (EGIDs) consist of eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE) and eosinophilic colitis (EC). EoE is characterized by eosinophilic infiltration of the gastrointestinal mucosa isolated to the esophagus and is considered a distinct entity from EG, EGE, and EC. While EoE has been rising in both prevalence and incidence, the other EGIDs (EG, EGE and EC) are significantly less common. Recent estimates suggest the prevalence of eosinophilic gastritis and gastroenteritis in the United States is 22 to 28 per 100,000 persons.[1]

In EG/EGE, eosinophils infiltrate the gastric or gastric/intestinal tissue. Multiple layers of the bowel may be involved: mucosal, submucosal and serosal. The symptoms at presentation often correspond to the layer of bowel involved.[3,4,5,6] The most common symptoms include abdominal pain, nausea, vomiting, early satiety, weight loss and diarrhea.

While treatment with elimination and elemental diets are highly effective methods at reducing mucosal inflammation in participants with EoE, diet therapy has not been extensively studied in EG/EGE. Instead, treatment for EG/EGE has focused on systemically active immunosuppressive agents such as systemic corticosteroids. While these medications are very effective at reducing eosinophilic inflammation, long-term side effects limit their use for maintenance therapy. Due to the significant morbidity with these illnesses and paucity of data on effective and safe treatment options, improved therapeutic options are needed.[2,3,7] Recently, there have been small case series suggesting that food allergens play a role in development of EG with 80% resolution with dietary therapy.[2] Unfortunately, there are no prospective studies using elemental diet in adults or children with EG/EGE.

Due to the paucity of controlled studies in EG and EGE, the pathophysiology is not as clearly defined as in EoE, which has been linked to food allergens in both the adult and pediatric populations.[7,8,9,10] Recent studies have suggested that EG/EGE is a systemic disorder involving blood and gastrointestinal tract eosinophilia, Th2 immunity and altered transcriptome distinct from EoE.[11, 12, 13]

1.2. Rationale for Selection of Investigational Product or Intervention

Given this background, we hypothesize that elemental diet, as a food allergen-free diet, will be an effective therapeutic option in EG and EGE in adults and will help reduce both histological and blood eosinophilia in these participants. This hypothesis will be addressed in the experiments of the following specific aims: (1) To determine the histologic improvement in tissue eosinophilia in participants with EG/EGE after treatment with a food allergen-free diet consisting of elemental formula and (2) To help identify clinical and histologic predictors of treatment response.

Participants who have a confirmed diagnosis of EG/EGE will be offered treatment with a food allergen-free diet. The diagnostic criteria for the disease will be participants with consistent clinical symptoms in addition to ≥30 eos/HPF in 5HPFs.[15,16,17] Other causes of mucosal eosinophilia will have been ruled out as per clinical care. For EG, mucosal biopsies will have to demonstrate a threshold number for diagnosis of ≥ 30 eosinophils/HPF in 5HPF from any gastric location. This number is based on the most comprehensive study of EG performed to date in which over 60 participants (50 adults, 10 children) were histologically studied.[17] For EGE, additional biopsies will have been taken from the duodenum demonstrating histologic eosinophilia (≥30 eosinophils/HPF).

Should this exploratory study reveal improvement as we suspect, this will provide participants with a much needed treatment alternative to systemic corticosteroids and will help to further delineate the pathophysiology of these important disorders.

1.3. Preclinical Experience

N/A

Clinical Studies

Recently, there have been small case series suggesting that food allergens play a role in development of EG with 80% resolution with dietary therapy.[2] Pilot data from our center in 15 adults with EG or EGE treated with a dietary therapy has shown promising results.[14] Of the 15 participant treated, 9 participants (60%) started with the Six Food Elimination Diet (SFED) whereas 6 (40%) began with an elemental diet (ED). Of the 9 SFED participants, 5 (56%) attained histologic resolution and all reported symptomatic improvement. All 4 of the participants who failed SFED attained histologic resolution upon switching to the ED. 100% of the participants who started with an ED attained histologic resolution in addition to symptomatic improvement. Eighty percent of the participants on the ED had endoscopic improvement, although none had complete endoscopic resolution. Since this time, we have had additional patients treated with dietary therapy with similar results. There are no other prospective studies using elemental diet in adults or children with EG/EGE.

2. Study Hypotheses/Objectives

2.1. Hypotheses

We hypothesize that a food allergen-free diet consisting of elemental (amino acid-based) formula will be an effective therapeutic option in EG and EGE in adults and will help reduce both histologic and blood eosinophilia in these participants.

2.2. Primary Objective(s)

If participants choose to undergo this form of dietary therapy, they will complete at least six weeks of nutritional intake consisting of an elemental (amino acid-based) formula as the source of their full nutrition. All participants will meet with a registered dietitian prior to the start of the therapy and nutritional goals will be identified and adapted for each individual patient. Standard of care (SOC) endoscopy will be performed after six weeks of treatment and biopsies will be evaluated for levels of eosinophils per high power field (eos/hpf). The primary objective of this protocol is to evaluate the effectiveness of a six-week elemental formula diet on the eos/hpf in participants with EG/EGE.

2.3. Secondary Objective(s)

We will evaluate clinical and histologic features to help determine any pretreatment predictors of response. Some clinical features we would evaluate include gender, age, duration of disease, atopic history, and baseline peripheral and mucosal eosinophil levels.

We anticipate that participants treated with a food allergen-free diet will have significant improvement in mucosal eosinophilia. We also anticipate improvement in symptoms, peripheral eosinophilia, endoscopic features, and quality of life scores. If participants undergoing this therapy improve significantly, dietary therapy will be substantiated as a viable therapeutic option for adults with EG/EGE. We will also be able to define the expected time course, endpoints and predictors of response to diet therapy in EG/EGE.

3. Study Design

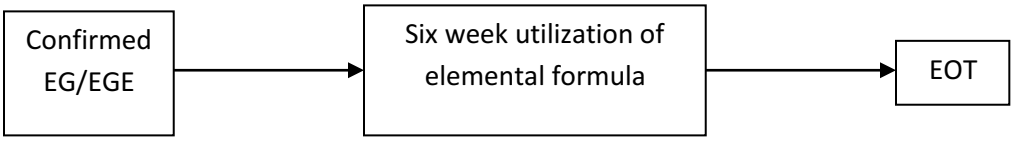
3.1. Description of Study Design

We will be recruiting 25 participants between the ages of 18 and 65 from the Northwestern Medicine outpatient GI Clinic and the Northwestern Memorial Hospital (NMH) GI Consult Service, as well as gastroenterology, allergy and multidisciplinary clinics of private and academic hospitals/outpatient medical practices in the United States. Participants will be enrolled in this study based on the presence of active EG/EGE and adherence to the inclusion and exclusion criteria.

Participants who have a confirmed diagnosis of EG/EGE will be offered treatment with food allergen-free diet. If participants choose to undergo this form of dietary therapy, they will complete at least six weeks of nutritional intake

consisting of an elemental (amino acid-based) formula as the sole source of their full nutrition. Six weeks has been the typical timeframe for diet therapy in EoE.[14]

FIGURE 1: STUDY DESIGN FLOWCHART



3.2. Primary Endpoint(s)/Outcome(s)

This prospective clinical trial will evaluate the effectiveness of a food allergen-free diet via utilization of elemental formula in adults with EG/EGE. The primary endpoint will be improvement in eosinophilic inflammation as determined by percent of patients who have achieved completed remission. Complete histologic remission will be defined as normalization of mucosal eosinophilia (histology with less than the diagnostic threshold levels of mucosal eosinophilia (<30 eos/HPF) in patients with a historical endoscopy being used as their baseline endoscopy, their initial slides will be used for assessment of their baseline histologic activity. The pathologist will be blinded to the patient's treatment but will be aware of their overall diagnosis.

3.3. Secondary Endpoint(s)/Outcome(s)

Secondary endpoints will be mean percent change in eosinophil density defined as (baseline absolute peak eosinophil density - final absolute peak eosinophil density)/baseline absolute peak eosinophil density; percentage of patients who have had partial histologic remission defined as a 50% reduction in baseline mucosal eosinophilia; and improvement in symptoms, endoscopic features, peripheral eosinophilia, and quality of life scores. As with the primary endpoint, initial slides will be used for assessment of baseline histologic activity for patients with a historical endoscopy being used as their baseline endoscopy, with the pathologist blinded to the patient's treatment but aware of their overall diagnosis. For the other secondary endpoints, we will utilize validated PRO instruments.

3.4. Exploratory Endpoint(s)/Outcome(s)

For those participants wishing to undergo food reintroduction to determine their culprit allergen, data will be collected prospectively.

3.5. Stratification, Randomization, and Blinding/Masking

3.5.1. Procedures for Unblinding/Unmasking

N/A

4. Selection of Participants and Clinical Sites/Laboratories

4.1. Rationale for Study Population

EoE is one of the subsets of EGID and has been shown to be a food allergy driven disease in both adults and children, resolving after treatment with an elemental formula diet. There are small case series suggesting that food allergens play a role in development of EG/EGE with 80% resolution with dietary therapy.[2,14] However, other than a small pilot study looking at a six food elimination diet and an elemental diet,[14] no prospective studies using elemental diet in adults or children with EG/EGE exist. Our preliminary data from that pilot study suggest that a food allergen-free diet utilizing elemental formula is effective in adults with EGID.

4.2. Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Participant must be able to understand and provide informed consent
2. Males and Females ≥18 to 65 years of age;
3. Have diagnosis of EG/EGE
4. Have histologically confirmed active disease (≥)30 eosinophils/hpf
5. Symptomatic (have experienced symptoms within the last one month prior to enrollment). Common symptoms may include abdominal pain, nausea/vomiting, early satiety, diarrhea, weight loss.
6. Female participants of childbearing potential must have a negative pregnancy test upon study entry
7. Female participants with reproductive potential, must agree to use FDA approved methods of birth control for the duration of the study

4.3. Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol
2. Secondary causes of gastrointestinal and peripheral eosinophilia
3. Eosinophilic infiltration isolated to the esophagus.
4. Pregnancy
5. Immunodeficiency states.
6. Have been treated with topical swallowed steroids within the last 6 weeks or systemic steroids within the last 2 months unless repeat endoscopy is performed and shows active inflammation on these therapies in which case these medications will be allowed to be continued without dose escalation.
7. Have taken immunosuppression medication or immunomodulators within 2 months of the study unless the recent/baseline endoscopy has active histologic inflammation while on these medications. In this case, these medications will be permitted to be continued as long as dose is not escalated during the treatment phase.
8. Have been on an elemental diet previously for six weeks with follow up endoscopy completed.
9. Have participated in any investigative drug study within 6 weeks prior to study entry.
10. Unable to complete study procedures including endoscopy.
11. Hyponatremia
12. At risk for fluid or electrolyte imbalances during the study (e.g. on high dose or multiple diuretics, clinically significant renal insufficiency (decreased GFR), unusually high or low fluid volume intake that could result in electrolyte abnormalities)
13. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study

5. Known and Potential Risks and Benefits to Participants

5.1. Risks of Investigational Product or Intervention as cited in Investigator Brochure or Package Insert

5.2. Risks of Investigational Product or Intervention cited in Medical Literature

Not applicable.

5.3. Risks of Study Procedures

Treatment with Elemental Formula may lead to weight loss.

Minimal risk exists related to implementation of short-term dietary therapies in EG/EGE. Dietary instruction regarding the dietary therapy and nutrition-related recommendations will be provided by a Registered Dietitian to ensure nutritional adequacy.

Potential risks of non-compliance with recommended intake of elemental formula may result in dehydration, fluid imbalance, and/or electrolyte imbalances.

Study Survey

Each participant between the ages of 18 to 65 years old will be asked to complete several surveys. There are no foreseeable physical discomforts or significant risks related to answering the PROs or study questionnaires. However, some questions may be difficult or uncomfortable for participants to answer. Participants may refuse to answer any questions that they are uncomfortable with. The participants may also feel inconvenienced by completing the questionnaires.

Gastric and Duodenal Biopsies

The risks associated with collecting additional biopsies (up to a total of seven obtained from the proximal and/or distal esophagus, stomach and duodenum) for research at the time of each endoscopy include: bleeding at the site of tissue (biopsy) collection, and a small chance of perforation (hole) of the stomach, duodenum, or esophagus. Perforation is the most severe gastrointestinal complication, but generally it is self-resolving and poses no life-threatening risk. Transient bacteremia as a result of diagnostic UGI endoscopy has been reported at rates as high as 8%, but the frequency of infectious endocarditis and other clinical sequelae is extremely low, such that current American Heart Association and American Society for Gastrointestinal Endoscopy guidelines do not recommend antibiotic prophylaxis with diagnostic UGI endoscopy solely to prevent infectious endocarditis.[54-57] The risk of aspiration during endoscopy is miniscule. To minimize the risks of collecting additional biopsies during endoscopy, the procedure will be performed or supervised by a skilled endoscopist, and additional biopsies will only be collected if the endoscopist feels it is appropriate to do so. Some samples that are collected during an endoscopy for research purposes may be frozen and shipped to other hospitals, institutions, and testing companies for analysis. Data may also be shared. The data and/or samples will be de-identified per HIPPA and have no PHI associated with them. The data and/or samples will be used in a collaborative relationship between institutions, or testing companies receiving the data and/or samples. All of these samples will be shared under a MTA, or other applicable agreement.

Blood Draws

Risks associated with the collection of blood are bleeding, bruising, and swelling, dizziness, fainting and infection at the site where the blood is drawn. In general, these procedures will be performed by individuals with expert skills in phlebotomy. To minimize the additional risks associated with phlebotomy, blood will be obtained during the standard placement of intravenous lines when possible. The amount of blood drawn will adhere to institutional policy.

Saliva

No known risks

Urine pregnancy

No known risks

Stool Collection

No known risks

5.4 Standard of Care Procedures Associated with This Study

Esophagogastroduodenoscopy (EGD)

Endoscopy with biopsy is a well-established procedure. Few patients have unexpected or serious complications. Since it is considered standard of care for adult patients with EG/EGE to have an EGD with biopsies within a six week time frame

to monitor the disease when trialing new therapies (foods or medications), the EGDs with biopsies that are associated with this study are not study procedures. Endoscopies will be performed regardless of study participation as patients' standard of care, and additional endoscopic procedures will not be performed because of participation in this study. It is considered standard of care for biopsies to be collected from the esophagus, stomach, and duodenum during endoscopy, and biopsies from all of these sites will be collected during endoscopic. Biopsies collected from the stomach and duodenum are evaluated to determine study eligibility.

Allergy Evaluation

SOC for EG/EGE may include a referral to the allergy clinic for evaluation. All medical information obtained from those visits will be collected and entered into the participant binder.

Laboratory Evaluation

As part of SOC the following blood tests are completed: peripheral eosinophil level, serum IgE and a comprehensive metabolic panel and additional nutritional labs at the discretion of the treating physician. The results of the blood test will be obtained and entered in the participant binder

5.5 Potential Benefits

The potential benefits of this study are:

1. To help identify whether food allergy plays a role in the development of EG/EGE
2. Resolution of histology and symptoms associated with EG/EGE
3. Offer alternative therapeutic option for EG/EGE aside from systemically active immunosuppressive agents such as systemic corticosteroids that have long-term side effects
4. There are no guaranteed benefits for any study participant.

6. Investigational Agent /Device/Intervention

6.1. Investigational Agents/Devices/Interventions

Elemental formulas (e.g. EleCare Jr., Neocate Jr., Neocate Splash) are nutritionally complete amino acid-based medical food. These formulas are indicated in treatment for eosinophilic GI disorders. Because the elemental formula is hypoallergenic, amino acid- based medical food, there are no known foreseen risks. The formulas are free of any milk or soy proteins. Amino acids are the building blocks of protein; the protein in their simplest form should not cause an allergic reaction.

6.1.1. Investigational Agent #1

EleCare Jr.—Abbott Nutrition; Columbus, OH

Neocate Jr.—Nutricia; Gaithersburg, MD

Neocate Splash – Nutricia; Gaithersburg, MD

6.1.1.1. Formulation, Packaging, and Labeling

6.1.1.1.1 EleCare Jr. is a nutritionally complete amino acid-based medical food for severe food allergies and GI disorders. The medical food comes in a powder of 30 Calories per fluid ounce. The formula is packaged in 14.1 ounce (400 grams) cans. The powder should be mixed with water using the enclosed scoop; 5 fluid ounces of water with 4 scoops (38 grams) results in an approximate final volume of 6 fluid ounces or 7.5 fluid ounces of water mixed with 6 scoops (57 grams) of powder results in a final volume of 9 fluid ounces. The powder contains the following: Corn Syrup Solids (54%), High Oleic Safflower Oil (9%), Medium-Chain Triglycerides (8%), Soy Oil (7%), L-Glutamine (2%). Less than 2% of the

Following: L-Asparagine, L-Leucine, DATEM, L-Lysine Acetate, L-Valine, Calcium Phosphate, L-Isoleucine, Artificial Flavor, Potassium Phosphate, L-Arginine, L-Phenylalanine, L-Tyrosine, Potassium Citrate, Sodium Citrate, L-Threonine, L-Proline, L-Serine,

LAlanine, Magnesium Chloride, Glycine, L-Histidine, L-Methionine, Ascorbic Acid, Calcium Carbonate, LCystine Dihydrochloride, L-Tryptophan, Magnesium Phosphate, Choline Chloride, Aspartame, m-Inositol, Acesulfame K, Ferrous Sulfate, Taurine, Ascorbyl Palmitate, Zinc Sulfate, dl-Alpha-Tocopheryl Acetate, Sucralose, L-Carnitine, Niacinamide, Salt, Calcium Pantothenate, Manganese Sulfate, Thiamine Chloride Hydrochloride, Cupric Sulfate, Vitamin A Palmitate, Riboflavin, Pyridoxine Hydrochloride, Folic Acid, Beta-Carotene, Biotin, Phylloquinone, Chromium Chloride, Potassium Iodide, Sodium Selenate, Sodium Molybdate, Vitamin D3, and Cyanocobalamin. Allergens: Phenylketonurics: Contains phenylalanine

6.1.1.1.2 Neocate Jr. is a nutritionally complete, powdered amino acid-based medical food. The standard dilution is 1 kcal/mL. Each can contained 14.1 ounces. The powder contains: Corn Syrup Solids (52%), Refined Vegetable Oil (Palm Kernel and/or Coconut Oil (8%), Canola Oil (8%), High Oleic Safflower Oil (8%)), L-Arginine (2.4%), L-Glutamine (2.3%), L-Lysine L-Aspartate (2%), and less than 2% of each of the following: Tripotassium Citrate, Calcium Phosphate Dibasic, L-Leucine, L-Phenylalanine, L-Proline, Silicon Dioxide, L-Valine, Glycine, L-Isoleucine, N-Acetyl-L-Methionine, L-Threonine, Mono and Diglycerides, Sodium Chloride, L-Histidine, L-Serine, L-Alanine, Magnesium Acetate, Calcium Phosphate Tribasic, Choline Bitartrate, L-Tryptophan, L-Tyrosine, Diacetyl Tartaric Acid Esters of Mono and Diglycerides, M-Inositol, L- Ascorbic Acid, L-Cystine, Propylene Glycol Alginate, Taurine, Ferrous Sulfate, L-Carnitine, Zinc Sulfate, DL-Alpha Tocopheryl Acetate, Niacinamide, Calcium D-Pantothenate, Manganese Sulfate, Cupric Sulfate, Riboflavin , Thiamin Chloride Hydrochloride, Pyridoxine Hydrochloride, Vitamin A Acetate, Folic Acid, Potassium Iodide, Chromium Chloride, Sodium Molybdate, Sodium Selenite, Phylloquinone, D-Biotin, Vitamin D 3, Cyanocobalamin.
The chocolate flavor contains: Artificial Flavor (7.2%), Sugar (4.7%), and less than 2% of the following: Artificial Sweetener: Sucralose.

6.1.1.1.3 Neocate Splash is a nutritionally complete, amino acid-based, ready-to-feed medical food. Each drink box contains 8 fluid ounces (237 mL). The formula contains:

Orange-Pineapple and **Grape** flavors:
Water, Maltodextrin, Sugar, Refined Vegetable Oils (High Oleic Sunflower Oil, Medium Chain Triglycerides (Modified Palm Kernel And/Or Coconut Oil), Canola Oil), and less than 2% of each of the following: Artificial Flavors, Calcium Glycerophosphate, Malic Acid, L-Arginine, L-Lysine L-Aspartate, Microcrystalline Cellulose, L-Leucine, Tripotassium Citrate, L-Phenylalanine, Diacetyl Tartaric Acid Esters Of Mono- and Diglycerides, Mono- and Diglycerides, Trisodium Citrate, L-Proline, L-Valine, Glycine, L-Isoleucine, N-Acetyl-L-Methionine, L-Threonine, L-Histidine, L-Serine, L-Alanine, Potassium Chloride, Magnesium Acetate, Choline Bitartrate, L-Tryptophan, Calcium Chloride, L-Tyrosine, Cellulose Gum, L-Ascorbic Acid, M-Inositol, L-Cystine, Sucralose, Ferrous Lactate, Taurine, L-Carnitine, Zinc Sulfate, DL-Alpha Tocopheryl Acetate, Niacinamide, Calcium D-Pantothenate, Manganese Sulfate, Sodium Selenite, Cupric Sulfate, Riboflavin, Chromium Chloride, Thiamin Chloride Hydrochloride, Vitamin A Palmitate, Pyridoxine Hydrochloride, Folic Acid, Potassium Iodide, Sodium Molybdate, Phylloquinone, D-Biotin, Vitamin D3, Cyanocobalamin.
Grape also contains less than 2% of Sucralose. Tropical Fruit also contains less than 2% of Acesulfame Potassium.

Tropical Fruit:
Water, Maltodextrin, Sugar, Refined Vegetable Oils (High Oleic Sunflower Oil, Medium Chain Triglycerides (Modified Palm Kernel And/Or Coconut Oil), Canola Oil), and less than 2% of each of the following: Artificial Flavor, Malic Acid, Calcium Glycerophosphate, L-Arginine, L-Lysine L-Aspartate, Microcrystalline Cellulose, L-Leucine, Tripotassium Citrate, L-Phenylalanine, Diacetyl Tartaric Acid Esters Of Mono- and Diglycerides, Mono- and Diglycerides, Trisodium Citrate, L-Proline, L-Valine, Glycine, L-Isoleucine, N-Acetyl-L-Methionine, L-Threonine, L-Histidine, L-Serine, L-Alanine, Potassium Chloride, Magnesium Acetate, Choline Bitartrate, L-Tryptophan, Calcium Chloride, L-Tyrosine, Cellulose Gum, L-Ascorbic Acid, M-Inositol, L-Cystine, Acesulfame

Potassium, Ferrous Lactate, Taurine, L-Carnitine, Zinc Sulfate, DL-Alpha Tocopheryl Acetate, Niacinamide, Calcium D-Pantothenate, Manganese Sulfate, Sodium Selenite, Cupric Sulfate, Riboflavin, Chromium Chloride, Thiamin Chloride Hydrochloride, Vitamin A Palmitate, Pyridoxine Hydrochloride, Folic Acid, Potassium Iodide, Sodium Molybdate, Phylloquinone, D-Biotin, Vitamin D3, Cyanocobalamin.
Tropical Fruit also contains less than 2% of Sucralose.

6.1.1.2. Dosage, Preparation, and Administration

Dosage will be every day by mouth for at least 6 weeks. The product should be stored at room temperature.

Neocate Jr and Elecare Jr provide 30 calories/oz when mixed according to directions on the label (i.e. 1 scoop for every 1 oz of fluid). Meeting the nutritional needs of the adult in terms of calories and protein is dependent on the volume of formula prescribed and consumed. To meet nutritional needs, most adults will need to drink somewhere between 400-600 gm (1-1.5 cans) of formula daily. Neocate Splash provides 237 calories (1 calorie per 1 mL) per each box consumed. The exact amount of formula, (Neocate Jr, Elecare Jr and/or Neocate Splash) needed daily will be determined on an individual participant basis with the dietitian to ensure adequate intake. Each adult participant will receive information on their nutritional needs and how to titrate the final volume of formula in order to ensure adequacy.

While elemental formula will be the sole nutritional source for each participant, more than one formula may be used during the course of the six weeks. Subjects can meet nutritional needs with a mixture of both the powdered elemental formulas and the ready to drink formulas. Neocate Splash will be used only as a supplement to the powdered formulas and recommendations for consumption will be made based on the number of boxes to be consumed daily. When using Neocate Splash, the total amount of calories from this volume will be deducted from nutritional needs and the remaining calories will be provided by powdered elemental formulas. Neocate Splash is being offered as a supplement to provide variety of flavor, ease of travel and reduce palate fatigue among participants.

6.2. Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection.

Participants will be provided the nutritional formula.

6.3. Assessment of Participant Compliance with Investigational Agent

The dietitian will monitor all nutritional parameters to help assess the total nutrition requirements for the patients during the study period and will be in communication with the participant every week to assess adequate caloric and

nutritional intake and to assure they are adhering to the diet. Subjects will be asked to report their weight to monitor weight loss. Participants will be provided a digital scale.

6.4 Toxicity Prevention and Management
Not applicable.

6.5 Premature Discontinuation of Investigational Agent
Study therapy may be prematurely discontinued for any participant for any of the following reasons:

- if the participant cannot tolerate the elemental formula,
- if the investigator believes that the study treatment is no longer in the best interest of the participant,
- if the participant has lost more than 10% of their body weight by week 4 of the study,
- and if the participant becomes pregnant

7. Other Medications

7.1. Concomitant Medications
7.1.1. Protocol-mandated

N/A

7.1.2. Other permitted concomitant medications

Throughout the study duration, all participants are expected to maintain medications such as a PPI, oral or nasal allergy medications such as antihistamines and any asthma-related medications that were prescribed prior to study entry.

7.2. Prophylactic Medications
Not applicable.

7.3. Prohibited Medications
Prohibited medications include immunosuppressive agents such as systemic corticosteroids and immunomodulators.

7.4. Rescue Medications
There are no treatments that will be provided on study for “rescue therapy”.

8. Study Procedures
Participants will adhere to an elemental formula diet for at least 6 weeks. The assessments will be done via the study center unless otherwise specified.

8.1 Screening/Baseline (Visit V1)
The purpose of the screening period is to confirm eligibility to continue in the study.

The screening visit should occur at a maximum of four weeks and a minimum of one week prior to the Elemental Diet visit. A research staff member will perform the informed consent process. After obtaining informed consent, the following study procedures and information gathered from medical records will be performed and documented:

- Assess eligibility (inclusion and exclusion criteria)
- Collect Medical, surgical and diet history from participant
- CBC with differential, serum IgE, and comprehensive metabolic panel within one month of Visit 1 . Additional nutritional

labs may be obtained at the discretion of the treating physician.

- Collect Demographics (age, gender, race) from participant

- Physical exam performed by a study clinician
- Collect stool sample (if possible) from subjects who have consented to stool collection – This sample will be mailed or brought back to the study center by participant.
- Obtain up to 7 biopsies from the duodenum, stomach and esophagus for research purposes (taken during standard of care (SOC) EGD) – If the SOC EGD is not performed at the study center following consent, the research biopsies will not be obtained.
- Research lab samples.
    - Blood (6-10 mL) for future genetic testing
    - Saliva (1-2ml) for future genetic testing if participant refuses blood collection
- Assessment of concomitant medications and therapies
- Pregnancy Test (urine)

Biopsies for research may be taken during a participant's standard of care EGD. If the participant has had an EGD and biopsies performed prior to the screening visit, the results of the EGD may be used to determine eligibility if it falls within the 3 month period prior to enrollment. Other exclusion parameters regarding prior medication would apply. SOC EGDs performed at an institution other than the study center may be used as baseline if the corresponding pathology report and slides are available and the eosinophil counts meet the inclusion criterion of ≥30 eosinophils/hpf. In cases where the local pathologist has concerns regarding the eosinophil count, slides may be sent to the CRPC for review in order to verify eligibility.

The amount of blood drawn (clinical plus research) will follow the NIH clinical center guidelines "Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center" (May 26 2012).

Stool samples may be collected from participants who have consented to stool collection. Patients will have the option of bringing in stool sample prior to initiation of elemental diet.

8.2 Elemental Diet (Visit 2)

All participants that have meet all entry criteria and have completed the screening procedures will start the elemental diet.

- Re- Assess eligibility (inclusion and exclusion criteria)
- Measure vitals (blood pressure, heart rate, respiratory rate, temperature), height and weight
- Administer patient reported outcome questionnaires, which will include dietary questionnaires to measure *intake* of the food allergens and a food diary to assess baseline diet
- Assess concomitant medications and/or therapies
- Evaluation, education and counseling by registered dietitian on the use of the elemental diet
- Palatability trial of available nutrient formulations.
- Pregnancy test (urine)

The participants will be encouraged to call the PI and/or study coordinator if they have any questions, concerns, adverse events, or changes in medication.

8.3 Phone Visits

A study staff member will conduct weekly phone visits (at weeks 1, 2, 3, 4 and 5) in order to monitor participants' progress and assess caloric and nutritional intake is met.

Subjects will be asked to measure and report their weekly weight using a digital scale loaned to each subject during the enrollment/baseline visit. Scales will go home with subjects and they will be instructed to check their weight weekly on the day of the scheduled wellness checks. Subjects will be encouraged to weigh themselves under reproducible conditions (i.e. first thing in the morning). Weight and percentage of weight loss, if any, will be recorded during weekly phone wellness checks.

The ultimate goal of the nutrition assessment is to estimate calories and protein needed to meet nutritional needs and provide eucaloric diets.

If a subject loses approximately 5% within 2 weeks and they are consuming an inadequate calories and formula volume, the study RD will suggest changes in final volume of the formula as well as behavioral strategies to allow them to consume necessary volume of formula to prevent further weight loss. Questions about adherence to the formula and assessment of symptoms will be assessed to better protect the nutritional wellness of enrolled patients. If at any time there is a concern related to symptoms or weight loss the participant will be brought in for an unscheduled visit to have assessment by a study clinician. If by 4 weeks the subject has lost more than 10% of their body weight they will be withdrawn from the study.
Elemental formulas can have a bitter aftertaste. Subjects will be instructed to drink them cold as this helps to balance the taste. A list of acceptable flavor additions will be provided to patients to help flavor formulas and improve palatability.

The following procedures will occur during these phone visits:

- Assess con-med and/or con-therapy compliance
- Assess weight and any weight changes
- Assess adherence with volume of formula recommended
- Asses any symptoms that might result in failure to consume full recommended volume
- Assess AEs
- Determine compliance with treatment

8.4 End of Treatment or Early Withdrawal (V3)

For participants who have completed the 6 week elemental diet therapy or have withdrawn early from the study, the following procedures will occur:

- Measure vitals (blood pressure, heart rate, respiratory rate, temperature), height and weight
- Physical exam performed by a study clinician
- CBC with differential, complete metabolic panel. Additional nutritional labs may be obtained at the discretion of the treating physician.
- Collect stool sample (if possible) from subjects who have consented to stool collection.
- Administer patient reported outcome questionnaires
- Assess AEs
- Obtain up to 7 biopsies from the esophagus, stomach and duodenum for research purposes (taken during the SOC EGD at the study center)
- Research lab samples -
    - Blood (6-10 mL) for future genetic testing may be collected at this visit if not collected at the time of the

endoscopy

- Saliva (1-2ml) for future genetic testing may be collected at this visit if not collected at the time of endoscopy.

- Assess participant compliance with diet therapy and concomitant medications
  Pregnancy Test (urine)

If a participant withdraws from the study before completing 6 weeks of dietary therapy, the End of Treatment/Early Withdrawal visit should be conducted within one week of the participant's stopping dietary therapy.

8.5 Unscheduled Visits

If disease activity increases or other concerns arise between regularly scheduled visits, participants should be instructed to contact study personnel and may be asked to return to the study site for an "unscheduled" visit. If the subject cannot tolerate the 6 weeks of elemental formula they will complete an Early Withdrawal visit and be referred back to their physician.

8.6 Visit Windows

Study visits should take place within the time limits specified in Schedule of Assessments (Table 1): the designated visit window for each scheduled visit are also indicated on the Schedule of Assessments table.

8.7 Retrospective Chart Review

Once a participant has completed the study and has made the decision to do dietary reintroduction process with their primary clinician for EG/EGE to determine culprit allergens they are asked to provide consent for us to review, collect and store the data.

9. Mechanistic Assays

We will perform stool microbiome analysis including 16S ribosomal RNA sequencing for metagenomic analysis of bacterial flora.

We will perform gastric transcriptome analysis using RNA sequencing, aiming to determine the degree to which elemental formula reverses molecular abnormalities, and develop preliminary data about predictive transcripts, as well as transcripts that remain abnormal and may provide insight about mechanisms of relapse and chronicity.[11,12,13]

10. Biospecimen Storage

Blood, saliva, stool and/or biopsies will be collected and stored for future analysis. Specimens will be obtained at one of the participants' study visits. Whether the sample collected is blood, tissue, stool or saliva, samples will be de-identified at the site, processed, and stored at Cincinnati Children's Hospital and only stored and not processed at Northwestern Medical Hospital (NMH) for future use.

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1. Participant Completion

Participant completion for the study will be at the end of their post-dietary therapy assessment.

11.2 Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. Participant is unable to comply with the dietary restrictions.
3. Participant becomes pregnant.
4. The participant develops an SAE related to therapy
5. The participant is “lost to follow-up” (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
6. The participant dies.
7. The Investigator no longer believes participation is in the best interest of the participant.
8. The patient develops worsening clinical symptoms (such as excessive weight loss (as outlined in section8.3) not resolving with adjustment of the formula, worsening nutritional parameters not resolving with adjustment of the formula (as noted in section 8.3) while on the therapy and therefore it is determined by the investigator that the participation is no longer in the best interest of the patient.
9. If by 4 weeks the subject has lost more than 10% of their body weight they will be withdrawn from the study.

11.3 Participant Replacement

Participants will be replaced if they have discontinued/withdrawn from the study before completing the elemental diet and follow up SOC endoscopy. The additional participants will be enrolled in the same manner as all other participants. Participant numbers will not be re-used. For subjects that are replaced, their last data point will be carried forward. A sensitivity analysis will be performed that considers all dropout/withdrawals to be treatment failures.

11.4 Follow-up after Early Study Withdrawal

If a participant is withdrawn from the study for any reason, the participant will be asked to complete a final visit and/or final assessments. The participant will be referred for evaluation by their primary clinician for EG/EGE. Final standard of care assessments may include endoscopy with biopsy and routine blood draws (CBC with differential, comprehensive metabolic panel).

.

11.5 Study Stopping Rules

The study may be prematurely terminated for the following reasons:

1. Investigator or sponsor request to withdraw from study participation.
2. If four participants have lost more than 10% of their body weight by week 4 of the study,

4. Serious and/or persistent noncompliance by the investigator with the protocol or other local applicable regulatory guidelines in conducting the study.

3. IRB decision to terminate or suspend approval for the investigation or the investigator.

12. Safety Monitoring and Reporting

12.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of the FDA must be reported promptly (per Section 12.5.1, Reporting of Serious Adverse

Events and Adverse Events to DAIT/NIAID). Appropriate notifications will also be made to the DSMB, site principal investigator and the Institutional Review Board (IRB).

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0: http://ctep.cancer.gov/reporting/ctc.html.

Safety will be assessed through documentation of AEs, physical examination findings, vital signs and nutritional assessments

12.2 Definitions

12.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with:

Study therapy regimen

There are no known adverse events associated with the use of elemental formula.

Study mandated procedures

Esophagogastroduodenoscopy (EGD) Research Biopsies

Bleeding estimated > 5ml at the site of biopsy collection
Perforation of the stomach, duodenum or esophagus

Blood Draws
Fainting/Vasovagal events
Bruising at puncture site larger than 2 cm diameter
Bleeding from puncture site lasting more than 30 minutes
Swelling at puncture site larger than 2 cm

12.2.1.1 Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the investigational therapy regimen caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the formula and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.2 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in Elecare Jr., Neocate Jr, or Neocate Splash package insert or is not listed at the specificity, severity or rate of occurrence that has been observed; or is not consistent with the risk information described in the general investigational plan.

12.2.3 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or DAIT/NIAID, it results in any of the following outcomes (21 CFR 312.32(a)).

Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported whether it is considered treatment related or not.

A life-threatening event: An AE or SAR is considered “life-threatening” if, in the view of either the investigator or DAIT/NIAID, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

Inpatient hospitalization that is not deemed as a suspected adverse reaction (SAR) due to EG/EGE or prolongation of existing hospitalization.

Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Congenital anomaly or birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

In this study hospitalization due to EG/EGE will not be reported as SAE’s. Patients with EG/EGE may be routinely hospitalized due to their medical condition for a variety of reasons including complications of their disease including dehydration, electrolyte abnormalities, GI bleeding, bowel obstruction etc.

12.3 Grading and Attribution of Adverse Events

12.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 14, 2010. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Protocol Chair and has been deemed appropriate for the subject population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.
Grade 2 = moderate adverse event.
Grade 3 = severe and undesirable adverse event.
Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events, but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

12.3.2 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE case report form. Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 12.3.2

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Table 12.3.2, Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

12.4 Collection and Recording of Adverse Events

12.4.1 Collection Period

Adverse events (including SAEs) will be collected from the time of consent until a subject completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

12.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc.] .
- Receiving an unsolicited complaint from the subject.

- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, *Grading and Attribution of Adverse Events.*

12.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 12.2, *Definitions)* on the appropriate AE/SAE CRF regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

12.5 Reporting of Serious Adverse Events and Adverse Events

12.5.1 Reporting of Serious Adverse Events to Sponsor

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via SAE CRF. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report to the RDCRN Data Management and Coordinating Center (DMCC) and DAIT/NIAID all serious adverse events (see Section 12.2.3, Serious Adverse Event), regardless of relationship or expectedness within 24 hours of discovering the event.
For serious adverse events, all requested information on the AE/SAE CRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE CRF will be updated and submitted. AE/SAE reports should be reviewed by the investigator.

The study will utilize the DMCC Adverse Event Monitoring System. Upon entry of a SAE, themanagement system will immediately notify the Study Chair, site PIs, the NIAID Medical Officer (MO), and the DAIT Project Manager (PM) and any additional agencies (if applicable- industry sponsor, CTEP, etc.) of any reported adverse events.

Contact information for NIAID Medical Monitor:
Amanda Rudman Spergel, MD
5601 Fishers Lane, Rm 6B54
Bethesda, MD 20892
O-240-627-3840
C-240-380-0497

rudmana@niaid.nih.gov

Serious adverse events: The NIH appointed Medical Monitor (MRO) determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The Medical Monitor may request further information if necessary and possibly request changes to the protocol or consent form as a consequence of the adverse event. A back-up notification system is in place so that any delays in review by the Medical Monitor beyond a specified period of time are forwarded to a secondary reviewer. The management system maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study. SAEs will be captured beginning at the time the participant starts the elemental formula. Non-serious expected adverse events: Except those listed above as immediately reportable, non-

serious expected adverse events that are reported to or observed by the investigator or a member of his/her research team will be submitted to the DMCC in a timely fashion (within 20 working days). The events

will be presented in tabular form and given to the MRO and RDCRN DSMB on a bi-annual basis. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DMCC will post aggregate reports of all reported adverse events for site investigators and IRBs.

12.5.2 Reporting to Health Authority

After an adverse event requiring 24 hour reporting (per Section 12.5.1, *Reporting of Serious Adverse Events to Sponsor*) is submitted by the site investigator and assessed by DAIT/NIAID ,there are two options for DAIT/NIAID] to report the adverse event to the DSMB and Single IRB:

12.5.2.1 Annual Reporting

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 12.2.1.1, *Suspected Adverse Reaction,* and Section 12.2.2, *Unexpected Adverse Event*).
- Serious and not a suspected adverse reaction (see Section 12.2.1.1 *Suspected Adverse Reaction*).
- Pregnancies.

12.5.2.2 Expedited Safety Reporting

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

Category 1: **Serious and unexpected suspected adverse reaction** [**SUSAR]** (see Section 12.2.1.1, *Suspected Adverse Reaction* and Section 12.2.2, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).

The sponsor shall report any suspected adverse reaction that is both serious and unexpected. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug,
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Category 2: **Any findings from studies that suggests a significant human risk**

The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

DAIT/NIAID shall notify the appropriate health authorities within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

12.5.3 Reporting of Adverse Events to IRBs/IECs

Adverse events, including expedited reports, will be reported by CCHMC, in a timely fashion to the central IRB in accordance with applicable regulations and guidelines.

12.6 Pregnancy Reporting

The investigator shall be informed immediately of any pregnancy in a study subject. A pregnant subject shall be instructed to stop taking study medication. The investigator shall counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the pregnant subject shall continue until the conclusion of the pregnancy.

The investigator shall report to the Data Management and Coordination Center (DMCC*)* and DAIT/NIAID all pregnancies within 1 business day of becoming aware of the event using the CRF. All pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy CRF shall be updated and submitted to the Data Management and Coordination Center (DMCC*)* when details about the outcome are available.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities.

All pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion - an SAE shall be submitted to the Data Management and Coordination Center (DMCC*)* and DAIT/NIAID using the SAE reporting procedures described above.

12.7 Reporting of Other Safety Information

An investigator shall promptly notify the site IRB as well as the DMCC and DAIT/NIAID when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event. The DMCC will notify the central IRB.

12.8 Review of Safety Information

12.8.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the DMCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate CRFs.

In addition, the Medical Monitor shall review and make decisions on the causality and relatedness of the SAE and pregnancy reports received by the DMCC (See Sections 12.5.1, Reporting of Serious Adverse Events to DAIT/NIAID and 12.6, Pregnancy Reporting).

12.8.2 DSMB Review

The DMCC will provide the Data Safety Monitoring Board (DSMB) with listings of all SAEs on an ongoing basis, including quarterly reports of all SAEs. Furthermore, the DSMB will be informed of expedited reports of SAEs.

12.8.2.1 Planned DSMB Reviews

The NIAID DSMB shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of an Expedited Safety Report in a timely manner. An SAE which the Medical Monitor determines to be an unexpected safety risk will be sent to the SMC immediately.

12.8.2.2 *Ad hoc* DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, any occurrence of meeting one of the study stopping rules as described in Section 11.5 will trigger an ad hoc comprehensive DSMB Safety Review. After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- Any death that occurs in the study, which is possibly or definitely related to study treatment regimen.
- If four participants have lost more than 10% of their body weight by week 4 of the study,
- The occurrence of a Grade 3 or higher related and unexpected SAE in ***1*** or more of the study participants who have received a study treatment.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.8.2.2.1 Temporary Suspension of *enrollment* for *ad hoc* DSMB Safety Review

A temporary halt in enrollment will be implemented if an ad hoc DSMB safety review is required.

13. Statistical Considerations and Analytical Plan

13.1 Overview

Participants with EGIDs will receive orally administered elemental formula for a period of at least 6 weeks. The primary endpoints of the study will be completed at the end of the six week dietary intervention however participants who complete dietary intervention will still be followed by their clinicians and continue their clinical treatment with diet reintroduction at the discretion of the treating physician. Participants who choose to undergo diet reintroduction will be followed prospectively and data accrued for future analysis.

13.2 Endpoints/Outcomes

The primary outcome will be improvement in eosinophilic inflammation as determined by percentage of patients who have had complete histologic remission defined as normalization of mucosal eosinophilia (histology with less than the diagnostic threshold levels of mucosal eosinophilia (<30 eos/HPF)). Secondary endpoints will be mean percent change in eosinophil density defined as (baseline absolute peak eosinophil

density - final absolute peak eosinophil density)/baseline absolute peak eosinophil density and partial histologic remission defined as a 50% reduction in baseline mucosal eosinophilia. Absolute peak eos/hpf is defined as the peak value of eosinophils in the gastrointestinal epithelium as observed by a pathologist. Exploratory outcomes will examine improvement in symptoms, endoscopic features, peripheral eosinophilia, and quality of life scores. We will utilize validated patient reported outcome instruments.

13.3 Analysis Plan

13.3.1 Analysis Populations.

Since we anticipate a small (N=20) sample size for analyses, we will explore each one of the potential predictors one-at-a-time for association with outcome (as opposed to developing a full predictive model for outcome).

13.3.2 Primary Analysis of Primary Endpoint(s)/Outcome(s)

Analysis of the complete histologic remission endpoint will give the frequency (and proportion) of those meeting criteria for complete histologic remission as defined previously, and present relevant 95% confidence limits as appropriate. Given the small sample size, exact 95% confidence limits will be used. As we have limited pilot data on a baseline value for this outcome, we simply aim to attain an exact confidence interval with a lower bound of no less than 0.75 to further demonstrate the efficacy of ED in EG/EGE patients seen in our initial pilot study.

However, we will also compare the proportion of patients who achieve complete histologic remission to a reference value of 0.56, the proportion who achieved complete histologic remission in the SFED group in our pilot trial, to compare efficacy of ED in EG/EGE patients to other dietary therapy. A one sample proportions test will also be utilized to assess the difference in proportion of complete histologic remission compared to a value of 0.56 (the pilot value for the SFED diet). All analyses for the primary and secondary endpoints will assume a 5% level of significance[18].

13.3.3 Supportive Analyses of the Primary Endpoint(s)/Outcome(s)

Please see above.

13.3.4 Analyses of Secondary and Other Endpoint(s)/Outcome(s)

Analysis of mean percent change in eosinophil density endpoint as previously defined will consist of a paired t-test. Relevant statistical assumptions will be assessed, and in cases of violation of these assumptions (i.e., extreme skewness or non-normally distributed data), the nonparametric Wilcoxon signed-rank test will be employed.

Analyses of the partial histologic remission endpoint will give the frequency (and proportion) of those meeting criteria for partial histologic remission as defined previously. As we do not have prior comparison values for partial histologic remission from the pilot, we will present relevant 95% confidence limits as appropriate. Given the small sample size, exact 95% confidence limits will be used.

13.3.5 Analyses of Exploratory Endpoint(s)/Outcome(s)

Additional continuous variables (age, duration of disease) will be examined for association with the primary outcome measure via a series of Pearson sample correlation coefficients and relevant 95% confidence intervals. Scatter plots will aid in illustrating any strong associations observed, and in the case of violation(s) of parametric assumptions, a series of Spearman rank correlation coefficients will be used. Categorical variables (gender, atopic history, endoscopic features) will be assessed for association with the primary outcome via independent two-sample t-tests and/or analysis of variance (ANOVA), as

appropriate; in the case of violation of parametric assumption(s), the nonparametric Wilcoxon rank-sum and/or Kruskal-Wallis test will be employed. All analyses will assume a 5% level of significance.

13.3.6 Descriptive Analyses

13.4 Interim Analyses

Will be performed after recruitment and completion of ten participants.

13.5 Statistical Hypotheses

Hypotheses for the primary and secondary outcomes:

H1: There will be a significant proportion of the patients on the elemental diet who achieve partial histologic remission as previously defined. As we have limited pilot data on a baseline value for this outcome, we simply aim to attain an exact confidence interval with a lower bound of no less than 0.75 to further demonstrate the efficacy of ED in EG/EGE patients seen in our initial pilot study. However, we will also compare the proportion of patients who achieve complete histologic remission to a reference value of 0.56, the proportion who achieved complete histologic remission in the SFED group in our pilot trial, to compare efficacy of ED in EG/EGE patients to other dietary therapy. We expect to see a significantly higher proportion of patients treated with the ED who achieve complete histologic remission than the pilot SFED value of 0.56.

H2: There will be a significant decrease in eosinophil density as previously defined for patients on the elemental diet.

H3: There will be a significant proportion of the patients on the elemental diet who achieve partial histologic remission as previously defined. As we do not have pilot data on a baseline value for this outcome, we aim to show an exact confidence interval with a lower bound of no less than 0.75.

All analyses will assume a 5% level of significance.

13.6 Sample Size Considerations

We plan to recruit 25 participants for inclusion in the study; if we assume a conservative 20% dropout rate, we will have 20 participants with complete follow-up data. Under these assumptions and pilot data, an exact one proportions test has 80% power to detect a significant difference between a baseline success value of 0.56 (as seen in the SFED) and 0.85 (our minimum expected success rate for the ED). [18], For the secondary and exploratory outcomes, we will also have 80% power to detect a mean percent change of 0.7 standard deviations from baseline (a moderate to large change) with a paired t-test, a significant (5% level) sample correlation coefficient of 0.58, and a mean outcome difference of 1.32 standard deviations across two equally represented groups using an independent two-sample t-test.

14. Identification and Access to Source Data

14.1. Source Data

Source documents and source data are considered to be the original documentation where subject information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

14.2. Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID, the DMCC and their representatives, as well as to relevant health authorities. Authorized representatives as noted above

are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals.

15. Protocol Deviations

15.1. Protocol Deviation Definitions

15.1.1. Protocol Deviation

The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

15.1.2. Major Protocol Deviation (Protocol Violation)

A Protocol Violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

15.1.3. Non-Major Protocol Deviation

A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

15.2. Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

Upon determination that a protocol deviation (major or minor) has occurred, the study staff will a) notify the site Principal Investigator, b) notify the DMCC and c) will complete a Protocol Deviation form. The Protocol Deviation form will document at a minimum the date PD occurred, the date PD identified, a description of event, whether the deviation resulted in SAE/AE, the signature of PI, report to central IRB, and documentation of a corrective action plan. The DMCC and DAIT/NIAID may request discussion with the PI to determine the effect of the protocol deviation on the study participant and his/her further study participation, the effect of the protocol deviation on the overall study, and corrective actions. The PI will complete and sign the Protocol Deviation form and submit it to the DMCC and to the central IRB, per IRB regulations. Major protocol deviations will be reported to the DSMB by the NIAID Medical Monitor at the Medical Monitor's discretion.

16. Ethical Considerations and Compliance with Good Clinical Practice

16.1 Quality Control and Quality Assurance

The investigator is required to keep accurate records to ensure that the conduct of the study is fully documented. The investigator is required to ensure that all CRFs are completed for every participant entered in the trial.

The sponsor is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

The CRFs will be completed online via a web-based electronic data capture (EDC) system that has been validated and is compliant with Part 11 Title 21 of the Code of Federal Regulations. Study staff at the site will enter information into the electronic CRFs, and the data will be stored remotely at a central database. Data quality will be ensured through the EDC system's continuous monitoring of data and real-time detection and correction of errors. All elements of data entry (i.e., time, date, verbatim text, and the name of the person performing the data entry) will be recorded in an electronic audit trail to allow all changes in the database to be monitored and maintained in accordance with federal regulations.

16.2 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the Cincinnati Children's Hospital Medical Center IRB (CCHMC IRB), which will serve as the central IRB for the study. Any amendments to the protocol or to the consent materials will also be approved by the CCHMC IRB before they are implemented.

The investigator will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country and local-specific regulatory requirements prior to initiating the study. The investigator is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential participants/parents or legal guardians (e.g. advertisements or information that supports or supplements the informed consent) are reviewed and approved by the IRB. The investigator agrees to allow the IRB direct access to all relevant documents. The IRB must be constituted in accordance with all applicable regulatory requirements. The investigator will provide the IRB with relevant document(s)/data that are needed for approval of the study.

16.3 Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the delegation log will review the consent and answer questions. The consent designee must be listed on the delegation log, have knowledge of the study and received training (from the local IRB, PI, or study coordinator) in the consent process. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

This study will be conducted in compliance with ICH E6 GCP: Consolidated Guidelines pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, participants will give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. If the participant is unable to provide written informed consent, the participant's legally acceptable representative may provide written consent as approved by institutional specific guidelines. The informed consent document must be signed and dated by the participant, or the participant's legally authorized representative, prior to study participation. A copy of the informed consent document must be provided to the participant or the participant's legally authorized representative. Signed consent forms must remain in the participant's study file and be available for verification by the monitor, IRB, and/or regulatory authorities at any time. If participant's

legally acceptable representative provides written consent, participants will also give their written assent to participate in the study as approved by institutional specific obtaining assent.

The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

16.4 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

16.5 Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify the participant in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless the participant has consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if the participant consents to the disclosure, including for their medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research participants.

The certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the U.S. Department of Health and Human Services and/or the National Institutes of Health, which is finding this project or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA). The Certificate of Confidentiality does not prevent a participant from voluntarily releasing information about themselves or their involvement in this research, If a participant wants to research information released to an insurer, medical care provider, or any other person not connected with the research, the participant must provide consent to allow the researchers to release it.

Even with the Certificate of Confidentiality, the investigators continue to have ethical obligations to report child abuse or neglect and to prevent an individual from carrying out any threats to do serious harm to themselves or others. If keeping information private would immediately put the study participant or someone else in danger, the investigators would release information to protect the participant or another person. The Certificate of Confidentiality will also not be used to prevent disclosure as required by federal, state, or local law, such as reports of child abuse and neglect, or harm to self or others.

17. Investigator Requirements

17.1 Protocol Adherence

The investigator must adhere to the protocol as detailed in this document and agree that the Sponsor and the IRB must approve any change to the protocol. The investigator will be responsible for enrolling only those participants who have met the protocol screening and study entry criteria.

17.2 Case Report Forms

The CRFs will be used for the recording of all information and study data as specified by this protocol. The CRFs must be completed by the research personnel. The principal investigator is responsible for ensuring that accurate CRFs are completed in a timely manner. Collected data will be entered into online electronic case report forms. Electronic case report forms will be developed in collaboration with the Data Management and Coordinating Center that contain the requisite data fields.

17.3 Source Document Maintenance

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondence, computer printouts, clinical laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the investigator and made available for inspection by regulatory authorities. The original signed dated informed consent form for each participating participant shall be filed with records kept by the investigator and a copy given to the participant. The patient outcome questionnaires will be recorded directly on the paper forms and will be considered as source data.

17.4 Inspection of Records

Data generated by this study must be available for inspection by any regulatory authorities and the IRB as appropriate. At a participant's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Participant medical information obtained during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

17.5 Retention of Records

The investigator shall retain records required to be maintained under this part for a period of 2 years.

17.6 Data Quality and Monitoring Measures

As much as possible data quality is assessed at the data entry point using intelligent on-line data entry via visual basic designed screen forms. Data element constraints, whether independent range and/or format limitations or 'relative' referential integrity limitations, can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency.

- Data Monitoring: The RDCRN DMCC identifies missing or unclear data and generates a data query to the consortium administrator contact.
- Data Delinquency Tracking: The Data Management and Coordinating Center will monitor data delinquency on an ongoing basis.

17.7 Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. IRB approval for the protocol must be on file at the DMCC before accrual can occur from the clinical site.

The DMCC will use a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the subject. When the participant is registered to participate in the study, using the DMCC provided web-based registration system, the system will assign a participant ID number. Thus each participant will have two codes: the local one that can be used by the registering site to obtain personal identifiers and a second code assigned by the DMCC. For all data transfers to the DMCC both numbers will be required to uniquely identify the subject. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry since the numbers should match to properly identify the participant. In this fashion, no personal identifiers would be accessible to the DMCC.

17.8 Data Entry

Data will be collected either electronically (i.e. via tablet/computer) or on paper CRFs at each site and entered into online electronic case report forms maintained by the DMCC.

17.9 Laboratory Data Flow

The DMCC will provide the study with a specimen database that allows tracking of the collection, storage, and transfer of biological specimens, their submission to laboratories for testing, and the incorporation of laboratory results in the study database. The preferred method to exchange data electronically is through the Specimen Management System (SMS) Web Service. The Web Service allows laboratories to obtain specimen shipment information, receive individual specimens or specimen shipments, report specimen issues and communicate specimen aliquots in a secure manner (test result submission is planned).

17.10 Study Completion

Before a study can be considered completed or terminated, the investigator must have the following data and materials:

- Clinical laboratory findings, clinical data, and all special test results from screening through the EOT visit (to 30 days after the last dose of study agent).
- CRFs properly completed by appropriate study personnel and reviewed and approved by the investigator.
- Copies of protocol amendment(s) and IRB approval/notification if appropriate.
- A summary of the study prepared by the principal investigator (an IRB/IEC summary letter is acceptable).

17.11 Audits and Inspections

The principal investigator will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to CRFs and source data/documents.

17.12 Institutional Review Board Approval

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB for approval. IRB approval of the protocol, informed consent document, study materials and any advertisement (if applicable) used to recruit study participants must be obtained before the study may be initiated. This study will utilize a centralized IRB, and the IRB at Cincinnati Children's Hospital Medical Center will serve as the central IRB for the study.

The principal investigator (PI) is responsible for keeping the IRB advised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The PI is also responsible for notifying the IRB of any unanticipated AEs that occur during the study in accordance with local IRB policies. Recent guidance from the USA FDA suggests that the following AEs should be reported to the IRB/IEC as "unanticipated problems:"

- Any AE that, even without detailed analysis, represents a serious unexpected AE that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- A series of AEs that, on analysis, is both unanticipated and a problem for the study. There would be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and were significant to the rights and welfare of participants.
- An AE that is described or addressed in the IB/package insert, protocol, or informed consent documents, or is expected to occur in study participants at an anticipated rate (e.g., expected progression of disease, occurrence of events consistent with background rate in participant population), but occurs at a greater frequency or at greater severity than expected.
- Any other AE that would cause the sponsor to modify the investigator brochure, study protocol, or informed consent form, or would prompt other action by the IRB to assure protection of human participants.

It will be the responsibility of the investigator to assure that the essential documents are available at the investigator site. Any or all of these documents may be subject to, and should be available for, audit by CCHMC or Sponsor auditor and inspection by the regulatory authorities as defined in the monitoring plan.

18. Publication Policy

The CEGIR policy on the publication of study results will apply to this trial.

19. References

1. Spergel JM, Book WM, Mays, et al. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. Journal of Pediatric Gastroenterology and Nutrition. 2011 Mar;52(3):300-6.

2. Ko HM, Morotti RA, Yershov O, et al. Eosinophilic gastritis in children: clinicopathological correlation, disease course, and response to therapy. American Journal of Gastroenterology. 2014 Aug;109(8):1277-85.

3. Pineton de Chambrun G, Gonzalez F, Canva JY, et al. Natural History of eosinophilic gastroenteritis. Clinical Gastroenterology and Hepatology. 2011 Nov;9(11):950-956.e.1.

4. Chang JY, Choung RS, Lee RM, et al. A shift in the clinical spectrum of eosinophilic gastroenteritis toward the mucosal disease type. Clinical Gastroenterology and Hepatology. 2010 Aug;(8):669-75; quiz e88.

5. Reed C, Woosley JT, Dellon ES. Clinical characteristics, treatment outcomes, and resource utilization in children and adults with eosinophilic gastroenteritis. Digestive and Liver Disease. 2015 Mar;47(3):197-201.

6. Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic gastrointestinal diseases. Gastroenterology Clinics of North America. 2014 Jun; 43(2):257-68.

7. Kelly KJ. Eosinophilic gastroenteritis. Journal of Pediatric Gastroenterology and Nutrition. 2000; 30 Suppl:S28-35.

8. Kagalwalla AF, Sentongo TA, Ritz, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clinical Gastroenterology and Hepatology. 2006 Sep;4(9):1097-102.

9. Gonsalves N, Yang GY, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction indentifies causative factors. Gastroenerology. 2012 Jun;142(7):1451-9.e1; quiz e14-5.

10. Lucendo AJ, Serrano-Montalban B, Arias A, et al. Systemic Review: The Efficacy of Dietary Treatment for Inducing Disease Remission in Eosinophilic Gastroenteritis. Journal of Pediatric Gastroenterology and Nutrition. 2015 Feb 19. [Epub ahead of print].

11. Caldwell JM, Collins MH, Stucke EM, et al. Histologic eosinphilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, TH2 immunity, and a unique gastric transcriptome. Journal of Allergy and Clinical Immunology. 2015 Nov;134(5):1114-24.

12. Sherrill JD, Kiran KC, Blanchard C, et al. Analysis and expansion of the eosinophilic esophagitis transcriptome by RNA sequencing. Genes & Immunity. 2014 Sep;15(6):361-9.

13. Wen T, Stucke EM, Grotjan TM, et al. Molecular diagnosis of eosinophilic esophagitis by gene expression profiling. Gastroenterology. 2013 Dec;145(6):1289-99.

14. Gonsalves N, Doerfler B, Yang G, et al. A prospective clinical trial of six food elimination diet or elemental diet in the treatment of adults with eosinophilic gastroenteritis (abstract). Gastroenterology. 2009;136:S1861.

15. DeBrosse CW, Case JW, Putnam PE, et al. Quantity and distribution of eosinophils in the gastrointestinal tract of children. Pediatr Dev Pathol 2006;9:210-8.

16. Lowichik A, Weinberg AG. A quantitative evaluation of mucosal eosinophils in the pediatric gastrointestinal tract. Mod Pathol 1996;9:110-4.

17. Lwin T, Melton SD, Genta RM. Eosinophilic gastritis: histopathological characterization and quantification of the normal gastric eosinophil content. Mod Pathol 2011;24:556-63.

18. Cohen, J. A power primer. Psychol Bull. 1992;112(1): 155-159.

Table 1. Schedule of Assessments

	Screening /Baseline (Visit 1)	Elemental Diet (Visit 2)	Elemental Diet Phone Call	Elemental Diet Phone Call	Elemental Diet Phone Call	Elemental Diet Phone Call	Elemental Diet Phone Call	EOT/Early Withdrawal Visit 3
Week	Week -12 to -1	Week 0	Week 1 (±5 days)	Week 2 (±5 days)	Week 3 (±5 days)	Week 4 (±5 days)	Week 5 (±5 days)	Week 6 - 8
Informed Consent	X							
Questionnaires	X							X
Medical history	X							
Physical Examination	X							X
AE/ConMed Assessment	X	X	X	X	X	X	X	X
Results of SOC Allergy evaluation if completed								
Blood collection	X							X
Saliva collection for research	X							X
Stool collection for research	X							X
Research Biopsies (up to 7)	X							X
Diet education from Registered Dietician		X						
Diet follow up			X	X	X	X	X	X
SOC EGD with biopsy	X							X
Urine Pregnancy test	X	X						X
EREFs	X							X
Prospective Data collection of reintroduced foods								