

A Food Additive Removal Diet for Pediatric Eosinophilic Esophagitis (FREE)

Principal Investigator: James P. Franciosi, MD

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1-9	<p style="text-align: center;">v.2</p> Eliminated SST group. Eliminated previously required 8- week PPI trial. Added 4 week PPI washout period. Added 12 week swallowed steroid washout period. Extended duration of treatment to 12 weeks	ESPGHAN guidelines on EoE have recently changed. The diagnosis of PPIREE has been retracted as it is histologically indistinguishable from EoE. Therefore, PPIs are considered a treatment option, not a diagnostic prerequisite. Comparison of two diets and randomization to both groups ensures a comparison of the effects of eliminating additives vs traditional elimination diets, ensures equal allocation to groups, and reduces selection bias. A PPI and steroid washout period is recommended to determine the true severity of the esophagitis.
1,2,8	<p style="text-align: center;">v.3</p> Removed the additional biopsy	Investigators at our satellite sites expressed slight concern regarding the need to take an additional biopsy. The biopsy was dropped from the protocol as it was intended for future research and was not critical to this study.
5.1	<p style="text-align: center;">v.4</p> Limited time since diagnostic biopsy	To minimize changes in the eosinophil count since time of biopsy. Eight weeks was allowed because this is a realistic time frame for the next expected visit after the biopsy is taken.
1-4, 6, 8-9	Changed the nature and names of the diets	The feasibility of the diets was of some concern to the team, particularly difficulty recruiting, high drop-out, and

NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Protocol Template

		<p>the potential for nutritional deficiencies given that formula would not be allowed. Therefore, the study will compare a dairy free diet with dairy free plus additive free diet given that dairy accounts for the majority of allergic reactions. This will make the diets much more acceptable/feasible to the patients/parents and will still answer the question of whether food additives play a role in EoE.</p>
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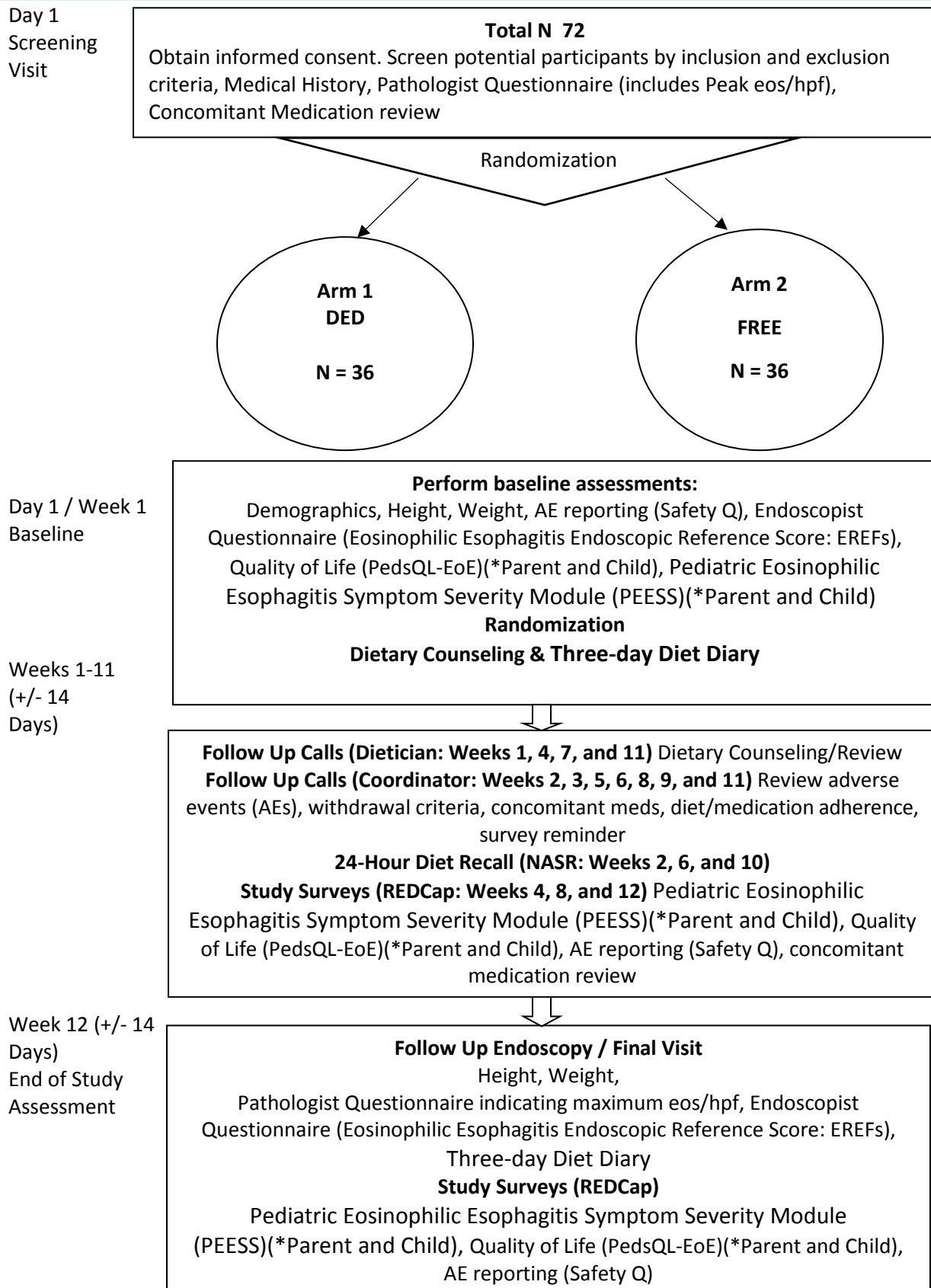
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Food Additive Removal Diet for Pediatric Eosinophilic Esophagitis (FREE)
Study Description:	Prospective, pragmatic standard of care clinical trial comparing dietary therapies of standard dairy elimination diet (DED) to standard dairy + food additive elimination diet (FREE) in children with eosinophilic esophagitis.
Objectives:	<p>Primary Objective: To compare histologic outcomes (eosinophils per high power field: eos/hpf) of standard dairy elimination diet (DED) to standard dairy + food additive elimination diet (FREE) in children with eosinophilic esophagitis.</p> <p>Secondary Objective: To compare endoscopic outcomes (Eosinophilic Esophagitis Endoscopic Reference scores: EREFs) of standard dairy elimination diet (DED) to standard dairy + food additive elimination diet (FREE) in children with eosinophilic esophagitis</p> <p>Tertiary Objectives: To compare symptomatic (Pediatric Eosinophilic Esophagitis Symptom Severity Module v2.0: PEESS) and quality of life (Peds-QL EoE Module 1) outcomes of standard dairy elimination diet (DED) to standard dairy + food additive elimination diet (FREE) in children with eosinophilic esophagitis</p>
Endpoints:	<p>Primary Endpoint: (1) Histologic change differences of maximum eos/hpf baseline vs 12 week endoscopy</p> <p>Secondary Endpoint: (1) EREFs: Eosinophilic Esophagitis Endoscopic Reference Score baseline vs 12 weeks</p> <p>Tertiary Endpoints: (1) Patient Reported Outcomes (Pediatric Eosinophilic Esophagitis Symptom Severity Module (PEESS) baseline vs 12 weeks, (2) quality of life (PedsQL-EoE)¹ baseline vs 12 weeks</p>
Study Population:	We will plan to enroll 72 patients over 4 sites each enrolling 18 patients per site in a 16-month period (approximately 1 patient per month per site) having 9 patients per site in each group (DED and FREE). Based on histologic primary outcome efficacy estimates of DED (50%) compared to FREE (estimated 70%) and a sample size of 36 enrolled patients per group

	<p>(72 total) with 88% power, we will be able to demonstrate a detectable difference of 30% among two group comparisons. We estimate a 20% drop out rate among the diet elimination groups and analysis based on intention to treat.</p> <p>Patients ≥ 5-≤ 17 years of age with isolated esophageal eosinophilia (≥ 15 eos/hpf). Patients with food impaction, peripheral eosinophilia $> 1,500 \mu\text{L}$, concomitant GI inflammatory conditions, history of upper GI tract surgery (e.g. fundoplication), acid reflux by pH probe, anaphylactic food allergies, severe developmental delay, taking recently prescribed inhaled corticosteroids or oral corticosteroids, have other medical conditions likely interfere with the study, has a significant psychiatric condition, has taken a PPI in the last 4 weeks, has taken swallowed steroids in the last 12 weeks, or are not fluent in spoken and written English will be excluded.</p>
<p>Description of Sites/Facilities Enrolling Participants:</p>	<p>Participants will be enrolled at: Nemours Children’s Hospital, Orlando, FL; Alfred I Dupont Hospital, Wilmington, DE; Seattle Children’s Hospital, Seattle, WA</p>
<p>Description of Study Intervention:</p>	<p>Once patients meet eligibility criteria, they will be randomized to DED or FREE study groups. Participants will receive dietary education. Lead dietitians from each site will be identified and the approaches to dietary education will be standardized. Dietary education will be completed at the baseline visit and during follow up phone calls throughout the study.</p>
<p>Study Duration:</p>	<p>We anticipate this study will take 30 months to complete.</p> <p>[December 31, 2017-----July 31, 2020]</p> <pre> Pre-trial Enrollment/Intervention Activities [-----] [-----] 7 mos 16 mos Data Collection [-----] 19 mos Data Analysis [-----] 4 mos </pre>
<p>Participant Duration:</p>	<p>Each participant will complete all study visits in 12 weeks +/-14 days.</p>

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES

Procedures	Screening Day -7 to 1	Enrollment/Baseline Visit 1, Day 1	Study Visit 2 (FUP Call) Day 7 (week 1) +/-2 days	Study Visit 3 (FUP Call) Day 14 (week 2) +/- 2 days	Study Visit 4 (FUP Call) Day 21 (week 3) +/-2 days	Study Visit 5 (FUP Call) Day 28(week 4) +/-2 days	Study Visit 6(FUP Call) Day 35 (week 5) +/-2 days	Study Visit 7 (FUP Call) Day 42 (week 6) +/-2 days	Study Visit 8 (FUP Call) Day 49 (week 7) +/-2 days	Study Visit 9 Day 56 (week 8) +/-14 days	Study Visit 10 Day 63 (week 9) +/-14	Study Visit 11 Day 70 (week 10) +/-14	Study Visit 12 Day 77 (week 11) +/-14	Study Visit 13 Day 84 (week 12) +/-14
Informed consent	X													
Review Inclusion/Exclusion Criteria	X													
Medical History	X													
Demographics		X												
Pathologist Questionnaire / Peak Eosinophils per high power field (Eos/hpf)	X													X
Randomization		X												
Personal Information		X												
Height and Weight		X												X
Endoscopist Questionnaire		X												X
Eosinophilic Esophagitis Endoscopic Reference Score (EREF)		X												X
Diet Education		X												
Dietician Follow Up Calls			X			X			X				X	
24-Hour Diet Recall (NASR)				X				X				X		
Three-day Diet Diary		X												X
Quality of Life (PedsQL EoE)(Parent & Child)		X				X*				X*				X*
Pediatric Eosinophilic Esophagitis Symptom Severity Module		X				X*				X*				X*

	Screening Day -7 to 1	Enrollment/Baseline Visit 1, Day 1	Study Visit 2 (FUP Call) Day 7 (week 1) +/-2 days	Study Visit 3 (FUP Call) Day 14 (week 2) +/- 2 days	Study Visit 4 (FUP Call) Day 21 (week 3) +/-2 days	Study Visit 5 (FUP Call) Day 28(week 4) +/-2 days	Study Visit 6(FUP Call) Day 35 (week 5) +/-2 days	Study Visit 7 (FUP Call) Day 42 (week 6) +/-2 days	Study Visit 8 (FUP Call) Day 49 (week 7) +/-2 days	Study Visit 9 Day 56 (week 8) +/-14 days	Study Visit 10 Day 63 (week 9) +/-14	Study Visit 11 Day 70 (week 10) +/-14	Study Visit 12 Day 77 (week 11) +/-14	Study Visit 13 Day 84 (week 12) +/-14
Procedures														
(PEESS)(Parent & Child)														
Adverse Event Reporting (Safety Q)		X				X*				X*				X*
Concomitant medication review	X	X		X	X		X	X		X			X	X
Coordinator Call				X	X		X	X		X	X		X	
Payment to Part. for Completed Visit		X				X				X				X

* REDCap survey – completed by participant/parent

2 INTRODUCTION

2.1 STUDY RATIONALE

Eosinophilic Esophagitis (EoE) is a food antigen driven inflammatory condition that continues to increase in prevalence. Commonly used food additives have been shown to promote intestinal inflammation in animal models², yet research is needed to further assess the impact of food additives on inflammatory conditions in humans. We hypothesize that dairy + food additive elimination (FREE) will show improved efficacy when compared dairy elimination alone (DED).

2.2 BACKGROUND

Eosinophilic esophagitis (EoE) is a chronic allergen driven inflammatory disorder histologically characterized by the abnormal infiltration of eosinophils in the esophagus (maximum eosinophil count ≥ 15). Primary symptoms manifest while eating and include dysphagia, chest pain, and food impaction. EoE was first described in the 1990s, but is increasingly recognized worldwide. It affects both adults and children with an estimated prevalence of 56.7/100,000.³

The treatment of EoE aims to reduce inflammation, thereby reducing symptoms. The recommended clinical pathway for the initial treatment of EoE includes high-dose proton pump inhibitor (PPI) therapy followed by either topical steroids or elimination diet in patients unresponsive to PPIs.⁴

PPIs: The relationship between acid suppression and EoE is unclear. Nevertheless, a subset of EoE patients are responsive to acid suppression medications such as PPIs (a condition referred to as Proton Pump Inhibitor Responsive Eosinophilic Esophagitis or PPIREE).^{5,6} PPIs may benefit patients with EoE by reducing acid or by an unclear anti-inflammatory mechanism. Because some patients are responsive to PPIs, the diagnosis of eosinophilic esophagitis has included the demonstration of persistent esophageal eosinophilia after a two-month course of high dose PPI therapy.⁴ However, ESPGHAN guidelines have recently changed and the diagnosis of PPIREE has been retracted as it is histologically indistinguishable from EoE. Therefore, PPIs are considered a treatment option, not a diagnostic prerequisite.

Steroids: Oral steroids, such as budesonide, are a preferable alternative to systemic steroids that have numerous and well documented adverse effects. Oral topical steroids have anti-inflammatory effects (i.e., fluticasone or budesonide, swallowed rather than inhaled, for an initial duration of 8 weeks) and are, therefore, another first-line pharmacologic therapy for the treatment of EoE.⁷

With the use of budesonide, studies show significant histological and symptomatic remission in 80-90% of patients.⁸⁻¹¹ Unfortunately, symptoms recur when steroids are discontinued. Although the majority of evidence suggests that adverse effects of short-term budesonide use are not common¹², several studies concluded that children treated with oral budesonide for one to six months experienced adrenal suppression.¹³⁻¹⁵

Dietary Treatments: Given that EoE is thought to be an antigen/immune-mediated disease, elimination diets are considered logical and safe first-line treatment options. Elimination diets focus on the removal of the allergens most likely to evoke the inflammatory response. Recent studies have demonstrated a response to elimination diets in 30-60% of EoE patients.^{16,17} The diets, however, vary regarding the number and types of foods eliminated. Three main strategies evolved in the last decade: (1) the elemental diet, which uses exclusively amino acid enteral formula, (2) the skin prick testing directed diet, which eliminates foods with positive allergy testing, and (3) empiric elimination in which the most common allergenic foods are avoided.²⁰ The elemental diet, although highly effective in inducing remission, is impractical for long term use given its high cost. In addition, refraining from eating any solid foods for an extended period of time is extremely difficult. Results regarding allergen directed diets have been mixed¹⁷ presumably because of the lack of reliability and specificity of allergy tests. Therefore, empirical elimination diets might be the easiest treatment option to implement and to maintain.

Elimination Diets and EoE: Studies have shown that a six-food elimination diet (6FED)(cow's milk, wheat, peanuts and tree nuts, soy, and fish/shellfish) induces remission in most children and adults with EoE¹⁷ but that only one in four patients sustain remission at nine months. Patients tend to relapse because the diet is difficult to follow and very restrictive. In addition, the 6FED includes a complex plan for the reintroduction of foods over specified time frames. A four-food elimination diet (4FED)(cow's milk, wheat, egg, and soy) is far less restrictive and more likely to encourage adherence. In addition, these four food groups appear to be the most commonly associated with the

inflammatory response in EoE patients.¹⁹⁻²⁰ Preliminary studies report a 54% histological remission rate with 4FED.²⁰⁻²² However, studies also show a 30-50% remission rate when eliminating dairy alone. More research is needed before concluding which diet is reliably effective in the majority of EoE patients.

The widespread use of food additives in modern-day diets might contribute to the increased incidence of inflammatory diseases such as EoE. Food additives are substances added during production, processing, packaging, or storage of food products. They are intended to enhance or preserve flavor, appearance, and durability. Some food additives are natural (e.g. vinegar for pickling, salted ham), but the additives of concern here are the artificial ones more recently introduced into the food supply.

Commonly used artificial food additives have been shown to promote intestinal inflammation in animal models². In addition, food additives are excluded from some diets that induce remission in Crohn's disease. In fact, the lack of food additives is likely one of the reasons enteral nutrition is so effective. As inflammatory bowel disease and eosinophilic esophagitis share GI tract mucosal immune dysregulation, dietary intervention with anti-inflammatory properties may be of benefit for patients with EoE.

There is a need to establish optimal treatment pathway(s) not only for the initial remission of EoE, but also for the long-term maintenance of remission. The adverse effects of long-term PPI and SST therapy are unknown. In addition, adherence rates to medications and to highly restrictive diets are poor. Elimination diets such as 4FED and FREE are less restrictive than other diets, which might improve outcomes. A preservative-free diet for EoE has not been evaluated. Finally, the current literature does not address patient reported outcomes or patient reported quality of life, which might be associated not only with efficacy, but also with rates of adherence, thereby impacting the sustainability of treatment.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Elimination diets: Elimination diets may affect nutritional status, eating pleasure, and quality of life.²³ However, again, given that the study duration is 8 weeks, significant nutritional deficiencies are unlikely.

2.3.2 KNOWN POTENTIAL BENEFITS

Elimination Diets: Benefits include relative safety and potential long-term maintenance. Recent studies have demonstrated a response to elimination diets in 30-60% of EoE patients. However the effects of the FREE diet have not been evaluate in patients with EoE.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This is a pragmatic trial comparing two standard of care treatments for EoE. Therefore, the risks are no greater than those ordinarily encountered in daily life. Furthermore, there is the prospect of benefit to enrolled patients (e.g. symptom reduction and improved quality of life). The risks are considered low and the benefit to the overall group of patients with EoE would be considered significant.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
<i>To compare histologic outcomes of DED and FREE among children with eosinophilic esophagitis</i>	Maximum eos/hpf (primary)	<i>Eosinophils are a biomarker of inflammation. Current diagnostic criteria specify ≥ 15 eos/hpf. A reduction in eos/hpf should correlate with a reduction in symptoms. A successful treatment outcome is < 15 eos/hpf.</i>
Secondary		
<i>To compare endoscopic outcomes DED and FREE among children with eosinophilic esophagitis</i>	Eosinophilic Esophagitis Endoscopic Reference Score (EREFs)(secondary)	<i>Includes additional eosinophil morphology and associated histopathologic features (e.g. degranulation, microabscesses, superficial layering, basal zone hyperplasia)</i>
Tertiary/Exploratory		
<i>To compare quality of life and patient reported outcomes of DED and FREE among children with eosinophilic esophagitis</i>	PedsQL-EoE (tertiary) Pediatric Eosinophilic Esophagitis Symptom Severity Module (PEESS) (tertiary)	<i>Determines the impact of DED and FREE on QOL and symptom severity, which is not routinely assessed.</i>

4 STUDY DESIGN

4.1 OVERALL DESIGN

Prospective, pragmatic standard of care clinical trial comparing dietary therapies of standard dairy elimination diet (DED) vs. standard dairy elimination and food additive elimination (FREE). After obtaining informed consent, participants will perform screening procedures. If all eligibility criteria are met, the patient will be randomized to one of the two diet regimens. Patients will receive dietary counseling at baseline. All participants will be followed via phone calls and REDCap surveys for the duration of the study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Food elimination diets have resulted in remission in an estimated 30-60% of patients. Typically, a six-food elimination diet is successful, yet it is difficult to maintain long-term adherence. Because the majority of allergens are found in four of these six foods, a four-food elimination diet has been suggested and demonstrated 60% remission in children in one study. Furthermore, other studies shown up to a 50% response rate when eliminating dairy alone. The dairy free diet has not been directly compared to a dairy free plus additive free diet.

4.3 END OF STUDY DEFINITION

The end of the study will be the point at which all required data has been collected or the date of the last patient visit.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB) approved written Parental Permission form is signed and dated by the parent or legal representative/caregiver.
2. An Institutional Review Board (IRB) approved written Assent form is signed and dated by the participant.
3. The participant/parent(s) or legal representative(s)/caregiver(s) are considered reliable and capable of adhering to the protocol call schedule and dietary requirements.
4. The participant is ≥ 5 years to ≤ 17 years of age.
5. The participant has isolated esophageal eosinophilia (>15 eos/hpf).
6. The biopsy used to diagnose eosinophilic esophagitis was taken no more than 8 weeks prior to the date of enrollment.
7. The family has access to the internet to complete weekly surveys and to a telephone to complete weekly follow up calls.

5.2 EXCLUSION CRITERIA

1. The participant has food impaction.
2. The participant has peripheral eosinophilia > 1,500 μ L
3. The participant has concomitant GI inflammatory conditions (e.g. celiac disease, inflammatory bowel disease).
4. The participant has a history of upper GI tract surgery (e.g. fundoplication)
5. Acid reflux by pH probe is suggested (*A pH probe is not required, but may be done as standard of care)
6. The participant has anaphylactic food allergies.
7. The participant has severe developmental delay that, in the opinion of the investigator, could jeopardize the participant's ability to participate in the study.
8. The participant is taking inhaled corticosteroids or oral corticosteroids for asthma, or has taken them in the last two months.
- 9 The participant has other significant medical conditions that, in the opinion of the provider, would impact the participant's ability to participate in the study.
10. The participant has a psychiatric condition that, in the opinion of the investigator, could jeopardize the participant's ability to participate in the study.
11. The participant does not speak or read English fluently.
12. The participant has taken a PPI in the last 4 weeks.
13. The participant has taken a swallowed steroid in the last 12 weeks.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Providers at participating sites will be educated on the study protocol. Pathologists will notify study coordinators of patient eligibility. M. Collin's recommended criteria for the diagnosis of eosinophilic esophagitis (EE) will be used to evaluate esophageal biopsies.²⁴ Two pediatric pathologists who have extensive experience in the diagnosis of EE will review all biopsies, blind to patient's dietary status. The grading and staging of EE will be based on Colin's criteria, especially to be focused on eosinophilic inflammation, epithelial basal zone changes, eosinophilic abscess, and lamina propria fibrosis. Interpersonal variation will be evaluated. Any biopsy with significant interpersonal variation will be re-reviewed by both pathologists to reach the reconciliation.

Patients (or in the case of children, the pediatric patient and their parent/legal guardian) will be approached for participation after a clinical assessment has been performed by a GI provider. Study procedures will be performed after obtaining proper consent and/or child assent. In addition, the clinic schedule will be reviewed each week for potential participants. If possible, patients or families will be contacted ahead of time to determine their interest in the study, should they qualify for participation.

Participants will be given a CT Payer card at the baseline visit. Participants will be paid the following: Baseline Visit \$25.00 + 2 weeks of surveys X \$25 + Final Visit \$50.00 = \$125.00 per participant. The telephone follow up and the participant questionnaires must be completed at each designated visit to receive payment. Stipends will be loaded onto the cards upon the completion of each visit.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Beginning from the date of enrollment/randomization, participation will last 12 weeks (+/- 14 days). Participants will be randomized to DED or FREE study groups. Participants will receive dietary education at the baseline visit.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

A randomization table will be generated for each site via *randomization.com* and will be used for assigning eligible participants to a treatment regimen.

To enroll a participant (Visit 1), the investigator (or designee) will assign each participant a 5-digit number which serves as the participant identifier throughout the study.

To randomize a participant (Visit 1), the investigator (or designee) will notify the lead site that a participant has been enrolled. The lead site will randomize the patient.

6.3 STUDY INTERVENTION COMPLIANCE

Study Coordinators will call participants/parents at weeks 2, 3, 5, 6, 8, and 10 to assess difficulty adhering to dietary protocols. If a participant is found to be persistently noncompliant with the diet, the investigator will make a decision as to whether the participant should be withdrawn from the study.

6.4 CONCOMITANT THERAPY

The following concomitant medications are prohibited during the study:

1. Inhaled corticosteroids or oral corticosteroids
2. Proton Pump Inhibitors (PPIs)

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Withdrawal criteria

Participants **must** be withdrawn from the study if any of the following events occur:

1. Participant experiences intolerable AEs, including clinically relevant abnormal laboratory findings that, in the opinion of the investigator, preclude further participation in the study.
2. Participants who are unable to tolerate study diet and/or for whom the provider discontinues study diet will be withdrawn from the study.
3. Participants unable or unwilling to adhere to dietary restrictions will be withdrawn from the study.
4. Investigator's decision that withdrawal from further participation would be in the participant's best interest.

Participants **may** be withdrawn from the study if any of the following events occur:

1. Participant has any clinically relevant change in medical or psychiatric condition and in the opinion of the investigator, the condition warrants discontinuation from the study.
2. Participant requires a medication that is not permitted by the protocol.

Investigators should attempt to obtain information for participants who withdraw or discontinue. For participants considered as lost to follow up, the investigator should make an effort (at least 1 phone call and 1 written message to the parent[s] or legal representative[s]/caregiver[s]), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The Case Report form (CRF) must document the primary reason for withdrawal or discontinuation.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

The participant and/or the parent(s)/legal representative(s) are free to withdraw the participant from the study at any time, without prejudice to continued care.

7.3 LOST TO FOLLOW-UP

Participants will be withdrawn from the study / considered LTFUP if the coordinator is unable to make contact by telephone to complete weekly assessments for at least 3 sequential weeks.

8 STUDY ASSESSMENTS AND PROCEDURES

At all visits and telephone contacts, participants will be instructed to call the investigator if any intolerable and/or serious AEs (SAEs) occur before the next visit or contact. After participants begin study medication, if any AEs necessitate a participant's withdrawal from the study, the participant should come in for a clinic visit as soon as possible after the occurrence of the AE. Planned clinic visits should be scheduled as indicated in Section 1.3

Screening/Baseline: Visit 1 (Day 1)

At Visit 1, participants will be evaluated for their suitability for enrollment. It is acceptable for this visit to be conducted on more than 1 day; however, all results of Visit 1 assessments should be available prior to randomization. Prior to the conduct of any study-related procedures, a complete explanation (both verbal and written) of the nature and purpose of the study will be given to the participant's parent(s)/legal representative(s) by the investigator (or designee). The parent(s)/legal representative(s) of the participant is required to sign and date the IRB approved informed consent if he/she decides to participate in the study.

The participant's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria, signature of an informed consent prior to any study-related procedures or evaluations, and the results of the following assessments.

Screening Procedures

1. Informed consent
2. Review Inclusion/exclusion criteria
3. Medical History
4. Demographics
5. Pathologist Questionnaire (*maximum eos/hpf)
6. Concomitant Medications

Baseline Procedures

1. Randomization
2. Endoscopist Questionnaire

3. EREF** score
4. PedsQL-EoE
5. PEES
6. Diet Counseling
7. Three-day diet diary
8. Concomitant Medications (review if baseline and screening visits do not take place on the same day)
9. Payment to Participant for Completed Visit

* Histological outcomes (e.g. maximum eos/hpf) will be compared and evaluated by two experienced study pathologists.

** All GI providers will be trained to assess EREFs prior to the initiation of the trial. They will complete the evaluation for all suspected cases of EoE.

Randomization

Participants will be randomized to either the DED or FREE diet.

Intervention

Participants will receive diet education. A trained nutritionist/dietician will provide counseling regarding the foods allowed and foods not allowed on each diet. Participants will be given written instructions and daily diet diaries for their own use.

Coordinator Telephone Contacts: (Weeks 2, 3, 5, 6, 8, 9, and 11; days 7 through 77)

Beginning with Telephone Contact at Day 7, the coordinator will assess AEs, review concomitant medications, review withdrawal criteria, and assess difficulty adhering to the diet. Participants will be sent invitations from REDCap to complete required questionnaires. The coordinator will remind participants to complete the questionnaires. The participant will be instructed to call the investigator if any intolerable and/or SAEs occur. If any change in the study medication is required, the participant should come in for a clinic visit as soon as possible.

Coordinator Call:

1. Diet/Medication Review & Adherence Assessment
2. Review concomitant medications
3. Review withdrawal criteria
4. Review previously reported AEs
5. Survey reminder

Participant Questionnaires (Baseline, Week 4, Week 8, and Week 12; days 1 through 84)

Participant Questionnaires (via REDCAP)

1. PEES
2. PedsQL-EoE

NASR 24 Hour Diet Recall (Weeks 2, 6, and 10)

The 24-Hour diet recall will be completed by the Nutrition Assessment Shared Resource (NASR). NASR was formed in 1993 and is engaged in human nutrition research and dietary assessment. They ensure a high degree of standardization, rigorous quality assurance and secure data management. NASR will complete three dietary assessments for each participant in the dietary intervention. These recalls will include foods eaten in the last 24 hours. NASR will provide detailed nutritional information as well as brand names for the detection of additives.

Final Assessment: (Week 12; day 84 +/- 14 days)

6. Pathologist Questionnaire (*maximum eos/hpf)
7. EREFs: Eosinophilic Esophagitis Endoscopic Reference Score)
8. PedsQL-EoE
9. PEES
10. Three-day diet diary
11. Review concomitant medications
12. Diet Review & Adherence Assessment
13. AE reporting

8.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An **Adverse Event (AE)** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation participant administered an investigational (medicinal) product and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.)

8.1.3 ADVERSE EVENT REPORTING

All adverse events will be reported to the principle investigator as soon as study staff are aware of the event. AEs that are not determined to be serious, will be recorded and reported to the IRB at the time of Continuing Review.

8.1.4 SERIOUS ADVERSE EVENT REPORTING

All SAEs will be reported to the lead coordinator/principle investigator within one business day of the first awareness of the event. The lead coordinator will complete the SAE CRF.

If the event meets fatal or life threatening criteria, it will be reported to the IRB within 24 hours of the first awareness of the event.

The Investigator must complete, sign and date the SAE CRFs and verify the accuracy of the information recorded on the SAE CRF with the corresponding source documents.

8.1.5 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

In the event of an unanticipated problem, the investigator must assess whether it is expected, whether it is related to the research, and whether it puts other participants at increased risk for harm.

8.1.6 UNANTICIPATED PROBLEM REPORTING

If the event is unexpected, related, and puts participants at increased risk, the lead coordinator will notify the IRB immediately via the submission of a Report of Unanticipated Problems.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Based on histologic primary outcome efficacy estimates DED without PPI therapy (50%) compared to FREE (estimated 70%) a sample size of 36 enrolled patients per group (72 total) with 88% power, we will be able to demonstrate a detectable difference between the three groups, we assume the standard deviation for both groups to be 30%. We hypothesize that changes in primary and secondary endpoints for FREE participants will be superior to DED.

9.2 SAMPLE SIZE DETERMINATION

The sample size was determined by pragmatic estimation of available EoE patients at each participating site. Data queries of EMRs were requested from respective IT departments to determine the number of EoE patients diagnosed in the past 12 months. Approximately 72 participants may be enrolled in the study in order to get an appropriate number of assessable participants.

9.3 POPULATIONS FOR ANALYSES

Safety analysis will be conducted on all patients evaluable for safety, defined as those patients who received any amount of study drug and provide any post-treatment safety data.

Efficacy analyses will be conducted on the intent-to-treat population, defined as all patients enrolled in the study who received patient IDs regardless of whether they received study drug or not.

9.4 STATISTICAL ANALYSES

Primary analyses will assess effectiveness endpoints, including eos/hpf and EREFs. Efficacy variables will be summarized descriptively and compared between treatment groups.

Secondary analyses include descriptive statistics of the patient population (patient demographics, clinical characteristics, and comorbid conditions), concomitant medications used in this patient population and changes to these treatments.

Categorical variables will be described using frequencies and percentages while continuous variables will be described using means, standard deviations, medians, and inter-quartile ranges.

Independent sample t-tests will be conducted to compare outcomes between groups.

Additional analysis plans may be developed based on clinical considerations.

9.4.1 SAFETY ANALYSES

Adverse events will be recorded. The number and percent of patient incidence of all AEs, AEs related to study drug, serious adverse events (SAEs), SAEs related to study drug, deaths during the study, and study drug discontinuations due to an AE or study withdrawals due to an AE will be calculated. Patient listings will be recorded for SAEs, deaths, and AEs leading to study drug discontinuation, or study withdrawals. Patients will be followed for 30 days after completion or study discontinuation for the occurrence of any SAE.

9.4.2 BASELINE DESCRIPTIVE STATISTICS

Demographic variables will include age, race, ethnicity, sex, height, and weight. Participant demographics will be summarized with descriptive statistics, as appropriate. Clinical characteristics will also be summarized.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent and assent forms (if applicable) will receive Institutional Review Board approval prior to initiation of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

10.1.1 INFORMED CONSENT PROCESS

Investigators will ensure that participants, or, in those situations where consent cannot be given by participants, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding the study.

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

The PPF for parent(s)/legally designated representative and the Assent Form for developmentally capable participants will be provided in English. Distinct assent forms are provided per age categories (7-11, 12-17). Site personnel authorized to participate in the consent/ assent process and/or to obtain consent/assent from the parent(s)/legally designated representative and participant will be listed on the Delegation of Authority form. The consent process will take place in a quiet, private exam room. Parent(s)/legally designated representatives and participants will be given ample time to review the consent forms and ask questions. A study physician will be available to answer medical questions or questions regarding alternative therapies.

The parent(s)/legally designated representative and/or participant must sign, personally date, and time (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) the PPF before any study-related procedures (i.e., any procedures required by the protocol) begin. The PPF/Assent must also be signed, personally dated, and timed (if the first study-mandated procedure is to be performed on the same day informed consent is obtained) by the authorized site personnel listed on the Delegation of Authority form.

A copy of the signed and dated PPF/Assent will be given to the parent(s)/legally designated representative; the original will be filed in the site documentation. The informed consent process as well as the assent process will be fully documented in the participant's medical records. This will include the study title, the participant number, the date and, if applicable, time when the participant's parent(s)/legally designated representative was first introduced to the study, the date of consent, who participated in the consent discussion, who consented the participant's parent(s)/legally designated representative, and any additional person present during the consent process (e.g., participant, any other family member), and a statement that a copy of the signed PPF/Assent has been given to the participant's parent(s)/legally designated representative.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The study starts with the first patient recruited (i.e., Informed Consent Form [ICF] signed) and ends with the last visit/contact of the last participant. The study is considered completed when the last participant completes the study (i.e. last final follow-up contact).

10.1.3 CONFIDENTIALITY AND PRIVACY

All efforts will be made to protect the privacy of individuals in this study. All health information and study data will be entered into REDCap. REDCap is a secure online database management tool. Only authorized users will have access to the study in REDCap. All authorized users will sign a REDCap user agreement. Data will be secured with a backup client.

10.1.4 DATA HANDLING AND RECORD KEEPING

Medical histories and demographics will be obtained through electronic medical record review, pathologist questionnaire, and endoscopic questionnaire. Data will be recorded by the enrolling site on a case reporting form (CRF) that will be filed and stored on site in the patient binder. Data will also be entered into REDCap by the site coordinator.

10.1.4.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Coordinators at each local site will enter CRF data into REDCap. The lead coordinator will monitor data completeness and query sites as needed. The Assistant Research Scientist will extract data from REDCap for analysis at the end of the study.

10.1.4.2 STUDY RECORDS RETENTION

The Investigator will retain copies of the approved protocol, completed CRFs, informed consent documents, relevant source documents and all other supporting documentation related to the project

for 7 years. These files will be made available for inspection upon reasonable request by authorized representatives of Sponsor and/or the relevant regulatory agencies.

10.1.4.3 FUTURE USE OF STORED SPECIMINS AND DATA

With the parent(s)/legally designated representative and participant's approval, de-identified biological samples will be stored at the Nemours' Center for Pharmacogenomics and Translational Research, Jacksonville, FL. These samples could be used to research the genetic causes of EoE, its complications and other conditions for which individuals with EoE are at increased risk, and to improve treatment.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research.

10.1.5 SAFETY MONITORING PLAN

Safety oversight will be under the direction of the PI. Adverse events will be reviewed immediately after they occur or are reported, with follow-up through resolution. The PI will also meet with GI providers and the lead coordinator once per month to review adverse events. The PI and GI providers will evaluate individual and cumulative participant data when making recommendations regarding the safe continuation of the study.

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

All research team members will take part in a 1-2 hour protocol training session. Documentation of training will be kept in the study binder. Subsequently, all research team members will take part in a bi-weekly conference call to discuss adherence to the protocol and review of the data received by the lead coordinator. Missing or invalid data will be discussed and, if possible, corrected by the lead coordinator. The lead coordinator and the PI will also review source files (consents, CRFs, questionnaires) for completeness and accuracy.

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