EIRB Protocol Template (Version 1.7)

1.0 General Information

***Please enter the full title of your study:**

Randomized Controlled Trial Comparing Fluticasone plus Omeprazole with Fluticasone alone in Eosinophilic Esophagitis

***Please enter the Protocol Number you would like to use to reference the protocol:**

RCT Fluticasone + Omeprazole vs Fluticasone
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary Dept?	Department Name
○	**P and R** - Walter Reed National Military Medical Center (WRNMMC)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

Min, Steve Bumjin

Select if applicable

☐ Student ☑ Site Chair
☐ Resident ☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

BAKER, THOMAS PATRICK
Associate Investigator
Daniels, Claire Patricia

Associate Investigator
Heisel, Matthew Owen, MD
Associate Investigator
Nylund, Cade Mccoy 2951446, MD, MS Lt Col
Associate Investigator
WELLS, Justin Matthew
Associate Investigator

B) Research Support Staff

MCCOWN, MICHAEL Yorke, DO
Monitor

3.3 *Please add a Protocol Contact:

Daniels, Claire Patricia
Min, Steve Bumjin

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 Is this a research study?

(•) Yes ( ) No

4.2 What type of research is this?

- [x] Biomedical Research
- [ ] Clinical trial (FDA regulated)
- [ ] Behavioral Research
- [ ] Educational Research
- [ ] Psychosocial Research
- [ ] Oral History
- [ ] Other

4.3 Are you conducting this project in pursuit of a personal degree?

( ) Yes (•) No

4.5 Is this human subjects research (Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an

investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by 32 CFR 219.101(a) (including exempt research involving human subjects) and DoDI 3216.02)?

(•) Yes ( ) No

4.6 Do you believe this human subjects research is exempt from IRB review?

( ) Yes (•) No

5.0 Personnel Details

5.1 List any Research Team members without EIRB access that are not previously entered in the protocol:

No records have been added

5.2 Will you have a Research Monitor for this study?

(•) Yes
( ) No
( ) N/A

Research Monitor Role:

The Research Monitor (RM) has the following responsibilities and the authority to:

1. Promptly reports any observations and findings to the Institutional Review Board (IRB), the Human Protections Administrator (HPA), or the Institutional Official;
2. Stops the research study in the presence of safety concerns for the human subjects involved in the protocol. The RM may remove human subjects from the study and take any others actions necessary to protect the subjects of the study. The RM may discuss the protocol with the investigators, interview human subjects, and consult with others outside the protocol about the research;
3. Reviews the study monitoring plans, review Adverse Events and determine their relatedness to the protocol, review Unanticipated Problems Involving Risks to Subjects of Others, make recommendations on changes to the informed consent process based on the review of study events, and review, and sign the continuing review report and other substantial submissions to the IRB.
4. May also observe recruitment, enrollment, consent procedures, and oversee study interventions.

If applicable, you may nominate an individual to serve as the Research Monitor:

	Selected Users
☐	MICHAEL Yorke MCCOWN, DO

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
: Other GME research funds - WRNMMC	: Other Intramural	6026

Total amount of funding:

6026

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

If Yes, complete and attach Conflict of Interest forms for all key personnel

8.0 Study Locations

8.1 Has another IRB/HRPP reviewed this study or will another IRB/HRPP be reviewing this study?

○ Yes ◉ No

IRB Name	Review Date	Determination
No records have been added		

8.2 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

○ Yes ◉ No

8.3 Study Facilities and Locations:

Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site
No records have been added						

Other:

Other		FWA or DoD	FWA or DoD		IRB

Institution Site	Site Role	Assurance Number	Expiration Date	Is there an agreement?	Reviewing for Site	
No records have been added						

8.4 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

8.5 Is this an OCONUS (Outside Continental United States) study?

○ Yes ◉ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

○ Yes ◉ No

9.0 Study Details

9.1 Abstract/ Summary:

Summarize the proposed study in 500 words or less, to include the purpose, the subject population, the study's design type, and procedures

2.1 Purpose
Evaluate the efficacy of concomitant therapy (or combination therapy) with omeprazole and swallowed fluticasone vs fluticasone therapy and placebo in the treatment of Eosinophilic Esophagitis.

2.2 Research Design
Double-blinded, Randomized Controlled Trial comparing the treatment group: omeprazole + swallowed fluticasone, with a control group: placebo + swallowed fluticasone. Primary outcome measured will be histologic assessment of esophageal tissue biopsies measuring number of eosinophils per high power field (eos/hpf). Secondary outcomes will be clinical and endoscopic and symptomatic changes following therapy using validated scoring measures and participant surveys, respectively.

2.3 Methodology /Technical Approach
Subjects that meet study inclusion criteria will be recruited from the Adult and Pediatric Gastroenterology clinics at WRNMMC through routine clinic visits, will meet with an investigator, and complete informed consent/assent. The participants will then complete a validated clinical symptom reporting tool - the Eosinophilic Esophagitis symptom activity index (EEsAI) for age 18 and above, or the Pediatric Quality of Life Inventory (PedsQL) for age 6-17yrs - and have their initial Esophagogastroduodenoscopy (EGD) images evaluated via a validated Endoscopic Reference Score (EREFS). Esophageal biopsies taken at patients initial EGD will be assessed by 2 designated blinded pathologists to record the number of eosinophils per high power field (HPF), as well as perform tissue immunohistochemical staining for eotaxin-3. Participants will be block randomized to treatment or control groups and complete 8 weeks of therapy, with a phone follow up at 4 weeks. At completion of 8 weeks of therapy, the participants will have repeat EGD with EREFs, biopsies evaluated for eosinoiphils/hpf and eotaxin-3 staining, and repeat EEsAI/PedsQL. We estimate a sample size of approximately 100 subjects.

9.2 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

eosinophilic, esophagitis, proton pump inhibitor, steroid

9.3 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Literature Review.

Eosinophilic esophagitis (EoE) is a disease of the esophagus characterized histologically by a disproportionate amount of eosinophils in the esophageal mucosa, as well as significant squamous epithelial hyperplasia. Clinical findings such as dysphagia, vomiting, abdominal pain, weight loss and feeding aversion are commonly seen in children, whereas adult symptoms typically include dysphagia and food impaction.(1) Characteristic histological and clinical findings are needed to diagnose EoE. Specifically, it requires greater than or equal to 15 eosinophils per high power field on esophageal mucosa biopsies, and a lack of symptom response to PPI treatment.(1) Prevalence of EoE is estimated at 56.7 per 100,000 people, with male:female ratio of approximately 3:1.(2)

A mainstay of treatment for EoE has been the use of corticosteroid therapy to suppress symptoms and reduce esophageal eosinophilia. An earlier study of patients with EoE that had failed to improve with traditional GERD treatment, demonstrated a significant decrease of esophageal eosinophils on biopsies and marked improvement in clinical symptoms following a 4-week course of oral methylprednisolone.(3) Additional studies have also shown significant clinical and histologic improvement in EoE with the use of prednisone.(4, 5) However, given the concerns behind long-term use of systemic steroids, topical steroid therapies for EoE have become the standard accepted alternative. Topical corticosteroids can be administered either in an oral viscous preparation, or nebulized and swallowed to coat the esophagus. The benefits of topical corticosteroid therapy for the treatment of EoE have been consistently demonstrated in the literature, including in various multiple randomized controlled trials (RCT). (6) Dohil et al, compared treatment with oral viscous budesonide (OVB) with placebo and found that 86.7% (13/15) of patients in the OVB group had significant decreases in esophageal eosinophilia, whereas none of the nine patients in the placebo group improved.(7) An additional RCT in children comparing nebulized and swallowed fluticasone treatment for EoE vs placebo showed 65% (15/23) of patients in the treatment group had complete resolution of eosinophilia on biopsy compared to none (0/13) of the placebo group.(8) Alexander et al, found that adults with EoE showed similar histologic improvement with fluticasone treatment, but not statistically significant symptom improvement compared to placebo.(9)

The role of acid suppression therapy with proton pump inhibitors (PPI) has significantly evolved over the past 10 years. Traditionally, PPI's have been used in EoE patients as a tool to fulfill the diagnostic guidelines for EoE, as well as a treatment for patients with EoE and GERD as a co-morbid disease.(1) However, many providers are unclear what exactly to do with the PPI once a diagnosis of EoE has been made. More recently, a new entity known as PPI-responsive esophageal eosinophilia (PPI-REE) was identified, in which a unique subset of patients with clinical, histologic and endoscopic manifestations of EoE, respond to PPI therapy as their sole treatment.(10) As a result of more studies suggesting that PPI's may affect esophageal eosinophilia by other mechanisms than acid blockade, the most recent EoE consensus guidelines updated their recommendations for PPI therapy to be used for patients, not only with co-morbid EoE and GERD, but also for those characterized as having PPI-REE.(1)

While the identification of this smaller subset of PPI-REE patients has brought upon a specific role for PPI therapy, its utilization in standard EoE treatment remains unclear. A recent randomized clinical trial comparing aerosolized swallowed fluticasone vs. omeprazole for patients with EoE showed no significant difference in esophageal eosinophilia with either treatment, but did result in a significant improvement in symptoms, based on Mayo Dysphagia Questionnaire responses, for patients treated with omeprazole.(11) This study seems to suggest a potential role in the use of PPI for treatment of standard EoE. Subsequent in-vitro research has also shed light into the pathogenesis behind PPI's therapeutic effects for EoE. For example, one mechanism for the recruitment of eosinophils to the esophagus is by a cytokine cascade that leads to the expression of the eosinophil chemoattractant, eotaxin-3, by esophageal epithelial cells.(12) Blanchard et al. were able to show that fluticasone down regulates the cytokine IL-13, as well as eotaxin-3 in patients with EoE.(13) Interestingly, Park et al. showed a similar mechanism of action with PPI's in that they decreased the expression of eotaxin-3 through acid-independent, anti-inflammatory mechanisms.(14) Most recently, Zhang, et al found even greater suppression of eotaxin-3 secretion in esophageal epithelial cells derived from patients with EoE, when they were treated with both fluticasone and omeprazole together, than when treated with either drug alone.(15) Thus, while topical corticosteroids remains the standard treatment for EoE, the specific role for PPI in the treatment of EoE continues to evolve in light of growing understanding of its pathogenesis.

Scientific Justification.

Little advancement in the treatment of EoE has been made in the past 20 years with continued reliance on topical steroids and food-trigger avoidance. Given the wide variety of histological and clinical

responses to EoE treatments, novel therapies are needed to better address patient symptoms and reduce tissue inflammation and remodeling. There is an overlap between GERD and EoE that is difficult to discern for many patients, causing clinicians to treat with a combination of standard therapies: topical steroids, food avoidance, and PPI therapy. Typically, patients will be placed on an initial course of PPI to rule out GERD as the primary or co-morbid cause of upper GI symptoms. Molecular studies by Zhang, et al suggest a synergistic relationship between topical steroids and PPIs by demonstrating increased suppression of eotaxin-3 secretion in esophageal epithelial cells derived from patients with EoE when they were treated with fluticasone and omeprazole together, than when treated with either drug alone. (15) The importance of the cytokine cascade in the pathophysiology of EoE cannot be understated. Ultimately, an in-vivo comparison to see whether PPI and topical steroid can translate into a histologic and clinical response in patients with EoE would be beneficial. To this date, a randomized clinical trial comparing concomitant therapy with PPI and fluticasone, to monotherapy with fluticasone alone, has not been done.

Human Subjects Justification.

Current clinical practice standards for EoE call for treatment with a topical steroid, which has been shown to decrease biopsy eosinophilia and clinical symptoms through a proposed suppression of the cytokine cascade involving the chemoattractant eotaxin-3. While a synergistic relationship between the topical steroid fluticasone and the PPI omeprazole has been demonstrated on a molecular level, with in vitro studies, it is unclear if the same relationship will exist in vivo. The translation from molecular cytokine suppression to histological and clinical symptom improvement has not been established and will be needed to drive therapy recommendations. A RCT comparing concomitant therapy for EoE with topical steroid + PPI vs Topical steroid + placebo will allow the clinical evaluation of a promising molecular study.

9.4 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions/hypotheses

Our aim is to compare the concomitant use of omeprazole plus swallowed fluticasone, to using swallowed fluticasone and placebo for the treatment of eosinophilic esophagitis.

Hypothesis: Combined therapy of swallowed fluticasone plus omeprazole for treatment of patients with eosinophilic esophagitis results in improved histology and symptoms as compared to swallowed steroid alone.

9.5 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

This study is a double-blinded, randomized controlled trial utilizing two study arms to evaluate the efficacy of concomitant therapy (or combination therapy) with omeprazole and swallowed fluticasone vs fluticasone therapy and placebo.

9.6 Target Population:

Describe the population to whom the study findings will be generalized

Male and non-pregnant female patients with a new diagnosis of eosinophilic esophagitis without co-morbid systemic or gastrointestinal inflammatory condition .

9.7 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

WRNMMC has a tradition of high quality research in the field of Eosinophilic Esophagitis (EoE) in both the adult and pediatric medicine services. This reputation has been earned through the hard work of previous investigators, as well as the development of unique multidisciplinary clinics, such as the EoE

Clinic, which is a collaboration between the Pediatric and Allergy departments. Our proposed study will shed light on novel treatment practices that may help to advance the treatment options for EoE and add to the reputation of WRNMMC as a leader in the field of EoE.

Study participants may benefit directly from participation by close evaluation and treatment with fluticasone in both treatment and control arms, which is an accepted standard medical treatment for patients with eosinophilic esophagitis, helping to relieve painful symptoms. They will also receive close follow-up throughout the study period, to ensure adherence to treatment.

10.0 Study Procedures, Data Management, and Privacy

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

Subjects will be recruited from the Adult and Pediatric Gastroenterology clinics at WRNMMC, during routine patient care appointments. Subjects will be screened and evaluated according to standard of care practices, based on their reason for referral and evaluation. The diagnosis of eosinophilic esopphagitis is most often made in children with poor weight gain or feeding disorders, while adults more typically present with food impactions or dysphagia. The diagnostic criteria for EoE as set forth by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition require that the patient be on an 8 week course of a high dose proton pump inhibitor prior to performing esopahgeal biopsies. Our study protocol follows the standard of care for diagnosis of EoE, which looks for > 15 eosinophils per high powered field. If the patients meets this criteria on biopsy as well as the study criteria, they will then have the opportunity to enroll in the study. Enrollment and randomization will not occur until the subject receives an 8 week course of PPI therapy prior to their initial EGD, and this EGD results in a diagnosis of EoE.

When it comes to treatment of EoE, the standard of care does not dictate whether or not the PPI should be continued. This decision is frequently made based on clinical preference and patient symptoms. This protocol will randomly assign the subject to the treatment arm that continues the PPI along with starting an inhaled steroid, or the treatment arm that uses a sham PPI and starts an inhaled steroid. The timing of biopsies and follow up EGDs will continue to follow the standard of care, which is after 8 weeks on therapy. However, there will be a few extra pieces of information gathered at that time that are not required by the standard of care. That will include patient questionnaires about symptoms, eotaxin staining, and scoring of endoscopic images. The details of the process are outlined below.

The participants who choose to consent and enroll in the study will then complete either the EEsAI (age 18 -60) or the PedsQL (age 6-17), both validated questionnaires that assess patient symptoms of EoE. Additionally, all study participants will have their initial Esophagogastroduodenoscopy (EGD) images evaluated via Endoscopic Reference Score (EREFS). This scoring system is a validated tool that has demonstrated moderate to good inter-observer variability. The PI for this protocol will be the physician who assigns a score to pre and post interention images, in order to limit variations between graders. The 6-8 esophageal biopsies taken at initial EGD will be evaluated by pathology per routine protocol to provide primary diagnosis. Again to limit variation, there are two pathologists serving on this protocol as AIs that will be evaluating the specimens obtained during this research period. Each set of biopsies will then evaluated by 1 of these 2 pathologists to record the number of eosinophils per high power field (HPF). Immunohistochemical staining on these biopsies for eotaxin-3 will be performed on the Ventana Ultra platform after stain optimization based on previously described protocols. Staining will be evaluated by 1 of 2 pathologists for intensity and percentage of cells staining (Allred scoring system). Dr. Baker will be performing research as a credentialed provider at WRNMMC Department of Pathology, although he is assigned to Joint Pathology Center.

The participants will be randomized into 2 groups: 1) omeprazole + swallowed fluticasone and 2) placebo + swallowed fluticasone. The placebo will replicate oral omeprazole. The study participants will be randomly assigned with concealment of allocation to one of the treatment groups, with each group having an equal number of participants (1:1 ratio).

Each treatment group will be treated for 8 weeks. Therapy for the PPI + topical steroid group will be 40mg omeprazole by mouth twice daily and 880mcg swallowed fluticasone twice daily. Therapy for the placebo + topical steroid group will be a sham omeprazole capsule by mouth twice daily and 880mcg nebulized and swallowed fluticasone twice daily (total dosage 1760 mcg). Participants will be instructed to take omeprazole or placebo on an empty stomach each morning, at least 30 minutes prior to eating, but no more than 60 minutes. Participants will also be instructed to rinse mouth with water or brush teeth after taking fluticasone, but not swallow anything within 30 minutes after taking the medication. For study participants age 17 years and younger, the dose for fluticasone will be 440mcg given 2-4 times per day based on 2011 consensus guidelines.(1) The pediatric dose for omeprazole will be 2mg/kg/day divided twice daily, with max dose of 40mg per day.

Compliance will be checked via phone follow up at 4 weeks and in person at 8 weeks (completion of therapy) by asking patient to report number of pills remaining and number of actuations remaining on the MDI. Participants will be given enough medication to last the full 8 weeks of therapy. At the time of repeat endoscopy, patients will be instructed to bring their medications for a full count of remaining pills.

At the end of 8 weeks of therapy, participants will undergo repeat EGD, with re-evaluation of all markers completed at the start of therapy including esophageal eosinophilia, endoscopic assessment (EREFS),validated clinical questionnaire (EEsAI or PedsQL), and immunohistochemistry staining for eotaxin-3. EGDs will be performed to standard of care, with biopsies taken from the esophagus only.

Prior to the EGDs, all pediatric subjects will undergo the routine pre-op evaluations and physicals by Pediatric GI and anesthesia, which is standard of care. All subjects are required to fast beginning the night prior to the EGD which is also standard practice.

The EGDs will be performed according to standard of care. All pediatric patients undergoing EGD for evaluation of symptoms consistent with abdominal pain, dysphagia, vomiting, poor weight gain, etc., have the same endoscopic investigation and biopsy specimens obtained, regardless of what is seen. It is also standard of care for all adult subjects presenting with symptoms suggestive of EoE (dysphagia, food impaction) to undergo upper endoscopic evaluation with esophageal biopsies. Biopsy specimens will be sent to pathology for standard histological examination. A single pathologist will be assigned to review all of the slides and corroborate the findings on any abnormal results.

EGDs will be performed using Olympus GIF140 or 160 endoscopes. Each subject will undergo all the standard pre-operative evaluations including physicals done by the pediatric GI provider and anesthesia. The type of sedation or general anesthesia will be based on the assessment by the anesthesia team responsible for the subject during the EGD. All pediatric patients undergoing an EGD will have the same endoscopic evaluation regardless of the indication for the procedure. It is standard practice to obtain biopsies from the duodenum, stomach and esophagus during the initial EGD, however, follow up EGDs will include only esophageal biopsies.

Esophageal biopsy specimens sent to pathology will be examined and reviewed by the pathologists. For each subject, the specific number of eosinophils per high power field (HPF) will be collected. As previously mentioned, 1 of 2 participating pathologists will be assigned to review all the slides, and corroborate the specific number of eosinophils. This data is also documented as part of the subjects routine care, and thus the results will be maintained in the AHLTA electronic record system as well. As an additional outcome measure, tissue eotaxin-3 level, will be measured independently by 1 of 2 pathologists on all subjects.

Assessment	**Visit/Follow up Interval**				
	Day of identification	**Within 2 weeks of consent**	**Week 4**	**Week 8**	**Week 8-10**
Screening/Informed consent /Discuss plan	**X**				
Randomization	**X**				
Demographics	**X**				
Pt completes clinical questionnaire	**X**				
Begin treatment	**X**				
PI/AI reviews initial endoscopy findings		**X**			

Path stain esophageal tissue for eotaxin-3		**X**			
Phone follow up for compliance check			**X**		
EGD				**X**	
Pt completes clinical questionnaire				**X**	
Path stain for eotaxin-3 on repeat biopsies					**X**
PI/AI reviews repeat endoscopy findings					**X**

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, how the data will be operationally measured, and approvals needed for use of information from DoD databases

Method of <u>Collection from Study Participants.</u>
- EEsAI or PedsQL (approval received for research use) standardized symptom questionnaires, based on age of participant, will be used to assess participant symptoms prior to treatment.
- Initial Esophagogastroduodenoscopy (EGD) images will be evaluated via Endoscopic Reference Score (EREFS) by investigators.
- Biopsies taken at initial EGD will be evaluated by pathology for number of eosinophils per high power field (HPF) and tissue eotaxin-3 level.
- Compliance will be checked via phone follow up at 4 weeks, and in person at 8 weeks (completion of therapy) by asking patient to report number of pills remaining and number of actuations remaining on the MDI.
- Participants will be given enough medication to last the full 8 weeks of therapy.
- At the end of 8 weeks of therapy, participants will undergo repeat EGD, with re-evaluation of all markers completed at the start of therapy: EREFS, EEsAI or PedsQL, and tissue for number of eosinophils per HPF and eotaxin-3 staining.

Study variables

a. Independent
    1. Standard therapy treatment group: Fluticasone topical steroid
    2. Intervention treatment group: Fluticasone topical steroid + PPI
b. Dependent
    1. EEsAI/PedsQL
    2. EREFS
    3. Eosinophils per high power field on esophageal biopsies
    4. Tissue eotaxin-3 IHC score from esophageal biopsies

10.3 At any point in the study, will you request, use, or access data from a DoD Database or the Military Health System (MHS)?

(•) Yes ( ) No

10.4 Review the definitions below and respond to the following two questions. If you are not sure of the answers, email DHA.PrivacyBoard@mail.mil for assistance.

The *Military Health System (MHS)* is defined as all DoD health plans and DoD health care providers that are organized under the management authority of, or in the case of covered individual providers, assigned to or employed by, the Defense Health Agency (DHA), the Army, the Navy, or the Air Force

***MHS workforce members* are employees, volunteers, trainees, and other persons whose conduct, in the performance of work for the MHS, is under the direct control of the MHS, whether or not they are paid by the MHS.**

***MHS business associates* are persons or entities that provide a service to the MHS and require protected health information (PHI) to provide the service.**

Are you an MHS workforce member?

(•) Yes, I am an MHS workforce member
( ) No, I am not an MHS workforce member

Are you an MHS business associate?

( ) Yes, I am an MHS business associate
(•) No, I am not an MHS business associate

10.5 Have you consulted with an MHS data expert to determine the data elements required for your study?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**dha.ncr.pcl.mbx.privacyboard@mail.mil**)

(•) Yes, then complete the questions below according to the data consult
( ) No, then complete the questions below according to the best of your knowledge

10.6 Indicate how you will request data from the MHS. Select all that apply.

[ ] Talking with MHS health care providers or MHS health plans about specific research participants
[ ] Obtaining MHS hard copy records specific to research participants
[x] Obtaining data from an MHS information system(s)

10.7 If you are obtaining data from an MHS information system(s), indicate whether you plan to receive a data extract or whether you plan to access an MHS information system directly to create a data set.

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should

be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

- [ ] Data Extract
- [x] Access

10.8 Do you intend to use only de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

- ○ Yes
- ◉ No

10.9 Indicate the MHS information system(s) from which you will seek to obtain data

If you do not know which system(s) contains the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or request guidance from an MHS data expert at: **DHA.PrivacyBoard@mail.mil**.

Below is a list of commonly used MHS systems. If the system from which you seek to obtain data is not listed below, list the name of the system in the "Other MHS Systems" category below
PHI Systems:

MHS Information System	Requesting Data
: AHLTA	: Yes
: CHCS	: Yes

PII-Only Systems:

MHS Information System	Requesting Data
No records have been added	

Information System	Requesting Data
No records have been added	

10.10 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- ◉ Yes, will merge data
- ○ No, will not merge data

10.11 Indicate the data elements about research participants or relatives, employers, or household members of the research participants that you will request from MHS hard copies or from MHS information systems.

If you answered "yes" to question 10.9 above, also indicate non-MHS data elements about research participants or relatives, employers, or household members of the research participants that you will have access to in any form or medium.

Data Element(s)	MHS	Non-MHS Systems	MHS Hard Copies

1. Names	☑	☐	☐
2. Postal address with only town, city, state and zip code	☐	☐	☐
3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000	☐	☐	☐
4. Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death	☑	☐	☐
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"	☐	☐	☐
6. Telephone numbers	☑	☐	☐
7. Fax numbers	☐	☐	☐
8. Electronic mail addresses	☐	☐	☐
9. Social Security numbers (SSNs)	☐	☐	☐
	☑	☐	☐

10. Medical record numbers			
11. Health plan beneficiary numbers	☐	☐	☐
12. Account numbers	☐	☐	☐
13. Certificate/license numbers	☐	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐	☐
15. Device identifiers and serial numbers	☐	☐	☐
16. Web Universal Resource Locators (URLs)	☐	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐	☐
18. Biometric identifiers, including finger and voice prints	☐	☐	☐
19. Full-face photographic images and any comparable images	☐	☐	☐
20. Any other unique identifying number, characteristic, or code (DEERs ID, EDIPN, Rank)	☑	☐	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

10.12 Do you believe it is possible for the MHS data to become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would use rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30, so the rank category may need to be expanded to include lower ranks.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 20 of the table above (in Section 10.10), but that could be used to identify an individual. Unique data elements include characteristics that are not themselves identifying, such as the rank of general or admiral, or a race or gender, but within the context of other information could be identifiable.

- ○ Yes, I believe there is a reasonable possibility the MHS data will become identifiable
- ◉ No, I believe there is no reasonable possibility the MHS data will become identifiable

10.13 HIPAA Privacy Rule and Use of Protected Health Information in Research:

- ○ N/A – will not use or disclose protected health information (PHI)
- ◉ HIPAA Authorization will be obtained
- ○ Use of a limited data set where a data use agreement will be obtained
- ○ Waiver/alteration of HIPAA Authorization is being requested

10.14 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

The investigators will be responsible for accessing and reviewing medical record data for those patients who have been consented and chosen to participate in the study. Subjects will be referred for enrollment by their primary gastroenterologist. No PHI will be removed from the covered entity by the research team in the course of the review. All data will be stored and organized on a password protected spreadsheet file where the subject will be identified by an alpha-numeric code, rather than a name. Research records must be kept for a minimum of three years after the research is completed and the study closed with the IRB (32 CFR 219.115(b)), and for this study we will keep the master list for 5 years after the closure of the study, while all de-identified data will be kept for a period of 10 years after the closure of the study. Consent forms will be retained for 7 years following closure of study, and HIPAA Authorization will be retained for at least 6 years from the date of its creation or the date when it was last in effect, whichever is later (45 CFR 164.530(j) (1)).

Specimens obtained during endoscopy will be transferred, stored and kept based on the standard operating procedure in the Pathology Department. There will be no changes to this standard for the purposes of this study.

10.15 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens /data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed.

The specimens and data collected during the study period will be accessible to the researcher for future research studies if the subject provides consent. The data will be stored for a 10 year period in a de-identified file as described above. According to the standard operating procedure of the Pathology Department, the specimens will be kept with patient identifiers for a period of 10 years. The researcher will not extend this period or make any changes to the protocol. Subjects may withdraw their data and specimens at any time. The subjects will not be contacted for future research, unless requested. There will not be any genetic testing done on these specimens.

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

See 11.4 below.

11.2 Sample Size:

The sample size was estimated for the primary outcome utilizing a two-sided likelihood ratio chi-square test of two independent proportions. The following parameters were used in this calculation: alpha of 0.05 and a power of 0.80 A response rate in the control group of fluticasone alone (reference proportion) was estimated to be 50% based on the study Konikoff et al.6 The estimated response rate for the treatment arms are is based on clinical experience as was estimated to be in the range of 70% to 80%. This graph demonstrates that the sample size estimation may vary anywhere from 78 to 180 subjects. We plan to enroll approximately 100 patients.

11.3 Total number of subjects requested (including records and specimens):

100

11.4 If you are recruiting by study arm, please identify the arms of the study and how many subjects will be enrolled in each arm

50 subjects in each arm - one arm will be fluticasone and placebo, one arm will be fluticasone and omeprazole.

11.5 Please provide a justification for your sample size

The sample size was estimated for the primary outcome utilizing a two-sided likelohood ratio chi-square test of two independent proportions. The following parameters were used in this calculation: alpha of 0.05 and a power of 0.8. A response rate in the control group of fluticasone alone (reference proportion) was estimated to be 50% based on the study Konikoff et al (6). The estimated response rate for the treatment arms are based on clinical experience as was estimated to be in the range of 70% to 80%. This graph demonstrates that the sample size estimation may vary anywhere from 78 to 180 subjects. We plan to enroll approximately 100 patients.

11.6 Data Analysis Plan:

Outcome variables are listed in the following table. All continuous data will be evaluated for normality of the data using both univariate methods, visual inspection, and the Kolmogorov Smirnov test. Differences in continuous data that is normally distributed will be tested using parametric tests and for data that is not normally distributed a nonparametric test. Likert scale data will be transformed into numerical data and evaluated as continuous variables.

Outcome variables	Variable Type	Statistical Test
Primary Outcome Tissue esophageal eosinphils < 15/ hpf	Binary categorical	Two-sided likelihood ratio chi-square test of two independent proportions

Change in EEsAI	Likert scale - continuous	Normally distributed data: t-test Non-normally distributed data: Mann-Whitney U
Change in PedsQL	Likert scale - continuous	Normally distributed data: t-test Non-normally distributed data: Mann-Whitney U
Change in EREFS	Continuous	Normally distributed data: t-test Non-normally distributed data: Mann-Whitney U
Change in eosinophils per hpf	Continuous	Normally distributed data: t-test Non-normally distributed data: Mann-Whitney U
Change in tissue eotaxin level	Continuous	Normally distributed data: t-test Non-normally distributed data: Mann-Whitney U

Although all outcomes will be evaluated and reported using pooled data, a priori planned subgroup analysis will include a stratification of the analysis and results based on adult and pediatric subject groups.

12.0 Participant Information

12.1 Subject Population:

-Male and female military health care beneficiaries age 6 to 60 years presenting with a new diagnosis of eosinophilic esophagitis.
-There will be no exclusion based on race or gender. Children will be included in this study given the fact that a significant number of patients diagnosed with EoE are identified during childhood and adolescence. The primary benefit for children enrolled in this study would be that they will be more closely tracked by a consistent nurse coordinator or GI provider to prevent loss of follow up and to ensure adherence to medications and treatment. The primary benefit for adults enrolled in this study would be more closely monitored care from a consistent nurse coordinator or GI provider to prevent loss of follow up and to ensure adherence to medications and treatment.

12.2 Age Range:

Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

- [x] 0-17
- [x] 18-24
- [x] 25-34
- [x] 35-44
- [x] 45-54
- [x] 55-64
- [ ] 65-74
- [ ] 75+

12.3 Gender:

- [x] Male

- [x] Female
- [ ] Other

12.4 Special categories, check all that apply

- [x] Minors /Children
- [ ] Students
- [ ] Employees - Civilian
- [ ] Employees - Contractor
- [ ] Resident/trainee
- [ ] Cadets /Midshipmen
- [x] Active Duty Military Personnel
- [ ] Wounded Warriors
- [ ] Economically Disadvantaged Persons
- [ ] Educationally Disadvantaged Persons
- [ ] Physically Challenged (Physical challenges include visual and/or auditory impairment)
- [ ] Persons with Impaired Decisional Capacity
- [ ] Prisoners
- [ ] Pregnant Women, Fetuses, and Neonates
- [ ] Non-English Speakers
- [ ] International Research involving Foreign Nationals - Headquarters Review is necessary

You must also consider the requirements of 45 CFR 46 Subpart D and DoDI 3216.02, Enclosure 3, paragraph 7.d.

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

12.5 Inclusion Criteria:

Order Number	Criteria
1	DEERS eligible
2	At least 6 years of age and < 60 years of age
3	presenting with initial diagnosis of EoE (symptoms may include dysphagia, abdominal pain, vomiting, gastroesophageal reflux, weight loss, feeding aversion)
4	require EGD as part of clinical evaluation

12.6 Exclusion Criteria:

Order Number	Criteria
1	age < 6 years or > or = 60 years
1	any concurrent or ongoing treatment with oral steroids.

2	any known diagnosis of a gastrointestinal inflammatory condition other than EoE. These conditions include ulcerative colitis, crohn's disease, celiac disease, and eosinophilic colitis.
3	pregnant women (due to increased risks for injury to the fetus during sedation/anesthesia screening for pregnancy is part of routine standard of care prior to procedures)
4	refusal to undergo endoscopy

13.0 Recruitment and Consent

13.1 Please describe the recruitment process, including how subjects will be identified and selected for the study.

Subjects will be recruited from the Adult and Pediatric Gastroenterology clinics at WRNMMC, during routine patient care appointments. Potential subjects will be identified by their primary gastroenterologist based on their clinical presentation and need for endoscopy. Once a subject is referred, they will be briefed on the study protocol by one of the investigators and given opportunities to ask any questions regarding the study. No HIPAA preparatory research will be required. If consent is provided, the subject will be enrolled in the study.

13.2 Compensation for Participation:

Study participants will not be compensated for their participation in the study.

13.3 Please describe the pre-screening process. If no pre-screening, enter Not Applicable in the text editor

Subjects will be identified through the primary Gastroenterologist in adult and pediatric gastroenterology clinics at Walter Reed National Military Medical Center. No HIPAA preparatory research provision will be required. Once a patient has been consented, the investigator will determine if the study subjects meets eligibility criteria.

13.4 Consent Process:

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

Once a subject has been referred, they will then meet with one of the GI nurses to schedule their EGD. At that time, an investigator will explain the study at length, answer any questions, and administer the informed consent. Subjects will be reminded that enrollment is purely voluntary and that they will receive the standard of care, regardless of whether they choose to enroll or not. The parent or guardian of children 6-17 years old will be asked to sign a consent form prior to study enrollment, and all questions will be answered. Any subjects between the ages of 8-17 years will also be provided an Assent

form to help provide additional age appropriate information regarding the study. If a subject turns 18 years old during the study time frame, he or she will need to be consented when they return for their next office visit.

13.5 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

- (•) N/A
- ( ) Propose ombudsman

13.6 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

In the consent form, the patient's right to withdraw from study participation is covered in detail. Subjects must notify the primary investigator via phone or email and return all study medication if they decide to withdraw. By leaving the study at any time, subjects will not risk losing their right to medical care or benefits within the military treatment facility. Subjects who withdraw will be referred to their primary gastroentetologist for continued care in accordance with acceptable standards of medical treatment.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

Research participants will not be exposed to any more risks than what are experienced by non-study patients being evaluated and treated for Eosinophilic Esophagitis. All interventions are within standard of care parameters in either treatment or control arm. It should be noted that there are risks associated with the EGD procedure to include bleeding, pain, infection, and intestinal perforation. There are also risks associated with the anesthetics used. However, patients who do not participate in the study would be subject to the same frequency and risks of EGD procedures.

14.2 Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

Safety Monitoring Plan
Participants will have cardiorespiratory monitoring throughout the endoscopic procedures, and will undergo pre procedure and post procedure monitoring per hospital protocol. The participant will receive a standard follow up call for biopsy results from the respective clinic, as is the standard of care for all patients who receive endoscopy. In addition, study participants will receive a telephone follow up 4 weeks after starting therapy.

Safety Analysis Plan
At the 4 week phone follow up, participants will be asked about any symptoms that have started since study treatment began. If worsening symptoms, patient will be brought in for a clinic visit to further evaluate ability to continue in trial.

14.3 Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e.g., child or spouse abuse

All hard copies of data will be kept in a locked file cabinet in the office of the PI at WRNMMC. The spreadsheet with EEsAI or PedsQL scores, EREFS score, histology and demographics will not include any names of the subjects, and will only be identified by numeric code. These codes will be randomly assigned by the PI, and the subjects identity will be stored electronically on the PIs password protected computer. Each unique subject code will be determined by whether they are an adult or pediatric subject, and their general chronological order of recruitment using only odd or even numerals (ie, P-5, A-22). All codes will be alphanumeric in nature.

All data will be stored and organized on a spreadsheet table. An alpha-num eric code will be assigned to each subject who will be used to identify the subject on the spreadsheet table. The PI will assign these codes, and PI and Research Monitor will only have access to the subject identifier codes on a master list. The research file will be stored electronically on the PIs password protected computer. The master list will be destroyed 5 years after study completion. All de-identified data related to the study will be destroyed 10 years after study completion.

14.4 Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

Study participants may benefit directly from participation by close evaluation and treatment with fluticasone in both treatment and control arms, which is an accepted standard medical treatment for patients with Eosinophilic Esophagitis, helping to relieve often-painful symptoms. They will also receive close follow up throughout the study period, to ensure adherence to treatment.

14.5 Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

No PHI will be removed from the covered entity by the research team in the course of the review. The PHI being used or disclosed is necessary for the research purposes. No research data, including Protected Health Information, will be sent outside of WRNMMC.

The subject's privacy will be protected by performing all study procedures in a private room; this includes obtaining consent and medical history, performing exams, and test. The only personnel that will be present will be the study investigator, study coordinator and staff, such as nurses, who will perform procedures under the direction of the study investigator. Any other persons will need explicit consent of the subject to be presented. The subject and his or her parents will be made to feel at ease by limiting the number of personnel present, and encouraging the subjects to ask question and notify the staff if he or she is uncomfortable in any way.

14.6 Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

Expected adverse events which are not serious are reported on the Continuing Review (CR) Progress Report. CR is generally performed on a 12-month cycle. More frequent Progress Reports will be provided at the discretion of the IRB.

Serious Adverse Events: The PI, within 24 hours, will report all related or possibly-related AND serious adverse events (SAE) occurring in subjects enrolled at WRNMMC. Serious adverse events will be reported even if the PI believes that the adverse events are unrelated to the protocol.

Unexpected (but not serious) adverse events occurring in subjects enrolled at WRNMMC which, in the opinion of the PI, are possibly related to participation AND places subjects or others at a greater risk of harm that was previously known or recognized in the protocol will be reported by the PI within 24 hours of discovery by email or phone to the IRB and the Research Monitor. A follow-up written report within 5 business days to the IRB and the Research Monitor is required.

Unanticipated problems involving risks to subjects or others (UPIRTSOs) will be reported to the IRB and Research Monitor via email or telephone within 24 hours of discovery and a written follow up report within 5 business days.

15.0 Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).

- ○ DSMP
- ○ DSMB
- ○ Both
- ◉ Not Applicable

16.0 Reportable Events

16.1 Reportable Events:

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

Reportable Events include adverse events (AE), serious adverse events (SAE), unanticipated problems involving risks to subjects or others (UPIRTSO), and protocol deviations as defined by the WRNMMC IRB Handbook.

UPIRTSOs, are unexpected AEs and SAEs, in the opinion of the PI, are possibly related to participation AND places subjects or others at a greater risk of harm that was previously known or recognized in the protocol and must be reported to the IRB and Research Monitor via email or telephone within 24 hours of discovery and a written follow up report within 5 business days.

Expected reportable events and events that are not related to study participation are reported on the Continuing Review (CR) Progress Report. CR is generally performed on a 12-month cycle. More frequent Progress Reports may be required at the discretion of the IRB.

When a deviation occurs, the investigator shall report the occurrence to the IRB. The investigator is required to make the determination whether the deviation meets the criteria for an unanticipated problem involving risks to subjects or others. The IRB Chair or IRB staff member shall also make the determination if the protocol deviation meets the definition of an unanticipated problem involving risks to participants or others. If the IRB Chair or IRB Staff member determines and documents that the deviation is an unanticipated problem involving risks to subjects or others or the deviation resulted from serious or continuing noncompliance, the IRB staff member shall place the deviation on the agenda of the next available IRB meeting for review. If the IRB Chair or IRB Staff member determines and documents that the deviation is not an unanticipated problem involving risks to subjects or others, the IRB Chair or staff member shall acknowledge the submission and complete the review through an administrative review procedure. Deviations that are determined to be minor as defined by the WRNMMC IRB Handbook are reported on the Continuing Review (CR) Progress Report.
As a reminder, according to DoDI 3216.02 (November 8, 2011), the IRB shall approve an independent research monitor by name for all DoD-conducted research involving human subjects, determined by the IRB to involve more than minimal risk to human subjects. Additionally, the research monitor may be identified by an investigator or appointed by an IRB or Institutional Official (IO) for research involving human subjects determined to involve minimal risk.

The research monitor may perform oversight functions and will report their observations to the IRB or a designated official. The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have the authority to stop a research protocol in progress, remove individual subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official. The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol, and they shall be independent of the team conducting the research involving human subjects

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs, dietary supplements, biologics, or devices be utilized in this study?

- [x] Drugs
- [ ] Dietary Supplements
- [ ] Biologics
- [ ] Devices
- [ ] N/A

18.2 Drugs, Dietary Supplements and Biologics/Vaccines details:

- [ ] Are drug(s) in this research being used in accordance to the approved labeling?
- [x] Are drug(s) in this research being used in a manner other than its approved labeling?

Enter Dietary Supplements and Biologics/Vaccines in the Drug Information table. Complete all relevant fields in the table ("Protocol Drug Details" screen). If the question is not relevant, leave the question blank and/or do not change the default selection.

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
⊟	**Trade Drug Name:** FLUTICASONE PROPRIONATE **Generic Drug Name:** **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	FLUTICASONE PROPRIONATE
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	WRNMMC Research Pharmacy
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Fluticasone is utilized off-label in the treatment of EoE. Nebulized and swallowed (topical)fluticasone treatment for EoE is accepted as a standard medical practice and is recommended as a first line treatment for EoE in both adult and pediatric consensus statements.(1, 16, 17) This study meets exemption criteria under 312.2b.1 under 21 CFR 312 and is not subject to FDA reporting requirements.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	BID

Route of administration:	Swallowed
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	
Identify who will be preparing the investigational drug/biologic for administration and describe in detail how it will be prepared:	Preparation will be in accordance with standard practices for WRNMMC pharmacy. No special handling is required.
Indication(s) under Investigation:	
Where will the drug be stored	WRNMMC pharmacy, in accordance with standard medication storing and dispensing practices.
Drug Storage Restrictions (including temperature, etc.):	As per indications on medication labeling.
Administration Instructions:	18 years old and above: swallow 4 puff of 220mcg fluticasone twice daily. Do not eat or drink within 30 minutes of swallowing. 6-17 years old: dose for fluticasone will be 220mcg given 4-8 times per day based on age, as recommended by expert consensus guidelines.
Possible Untoward Effects, Their Symptoms & Treatment:	Fatigue, malaise, headache, orophayngeal candidiasis, arthralgia, arthritis, musculoskeletal pain, sinus infection, sinusitis, upper respiratory tract infection, throat irritation, nasal congestion, nasopharyngitis, rhinitis, bronchitis, hypertension, subarachnoid hemorrhage, generalized pain, voice disorder, procedural pain, skin rash, pruritus, nausea and vomiting, viral gastrointestinal infection, gastrointestinal distress, gastrointestinal pain, toothache, malignant neoplasm of breast, influenza, abscess, muscle injury, back pain, herniated disk, cough, hoarseness, pharyngitis, upper respiratory tract inflammation, oropharyngeal pain, allergic rhinitis, fever, accidental injury, amputation, adrenocortical insufficiency, aggressive behavior, allergic skin reaction, aphonia, bacterial infection, bacterial reproductive infection, behavioral changes (very rare: includes hyperactivity and irritability in children), blepharoconjunctivitis, bronchospasm (immediate and delayed), cataract (long-term use), cholecystitis, Churg-Strauss syndrome, conjunctivitis, cranial nerve palsy, cushingoid appearance, decreased bone mineral density (long-term use), decreased linear skeletal growth rate (children and adolescents), dental caries, dental discoloration, depression, dermatitis, drug toxicity, eosinophilia, esophageal candidiasis, exacerbation of asthma, folliculitis, fungal infection, glaucoma (long-term use), hematoma, HPA-axis suppression, hypercorticoidism, hyperglycemia, hypersensitivity reaction (immediate and delayed; includes ear, nose, and throat allergic disorders, anaphylaxis, angioedema, bronchospasm, hypotension, skin rash, urticaria), increased intraocular pressure (long-term use), inflammation (musculoskeletal), keratitis, migraine, oral mucosa ulcer, osteonecrosis (especially with current or past use of systemic steroids), osteoporosis, paradoxical bronchospasm, photodermatitis, pneumonia, polyp (ear, nose, throat), pressure-induced disorder, soft tissue injury, urinary tract infection, vasculitis, viral skin infection. Treatment: discontinue use of medication.
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	None
Contraindications and Interactions, If Known:	Hypersensitivity to fluticasone.

Investigators Authorized to Prescribe:	Principal investigator and all associate investigators.

⊟	**Trade Drug Name:** Omeprazole **Generic Drug Name:** **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	Omeprazole
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	WRNMMC Research Pharmacy
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	This study meets exemption criteria under 312.2b.1 under 21 CFR 312 and is not subject to FDA reporting requirements.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	BID
Route of administration:	PO
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	
Identify who will be preparing the investigational drug/biologic for administration and describe in detail how it will be prepared:	Preparation will be in accordance with standard practices for WRNMMC pharmacy. No special handling is required.
Indication(s) under Investigation:	N/A
Where will the drug be stored	WRNMMC pharmacy, in accordance with standard medication storing and dispensing practices.
Drug Storage Restrictions (including temperature, etc.):	As per indications on medication labeling.
Administration Instructions:	18 years old and above: take one 40mg capsule or tab by mouth twice daily. 6-17 years old: 2mg/kg/day divided twice daily, with max dose of 40mg per day.

Possible Untoward Effects, Their Symptoms & Treatment:	Headache, dizziness, skin rash, abdominal pain, diarrhea, nausea, flatulence, vomiting, acid regurgitation, constipation, back pain, weakness, upper respiratory infection, cough, abdominal swelling, abnormal dreams, aggression, agranulocytosis, allergic reactions, alopecia, anaphylaxis, anemia, angina pectoris, angioedema, anorexia, apathy, arthralgia, atrophic gastritis, benign gastric polyps, blurred vision, bone fracture, bradycardia, bronchospasm, chest pain, cholestatic hepatitis, Clostridium difficile-associated diarrhea (CDAD), confusion, depression, dermatitis, diplopia, drowsiness, epistaxis, erythema multiforme, esophageal candidiasis, fecal discoloration, gastroduodenal carcinoids, glycosuria, gynecomastia, hallucinations, hematuria, hemolytic anemia, hepatic disease (hepatocellular, cholestatic, mixed), hepatic encephalopathy, hepatic failure, hepatic necrosis, hepatitis, hepatocellular hepatitis, hepatotoxicity (idiosyncratic), hyperhidrosis, hypersensitivity, hypertension, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, increased gamma glutamyl transferase, increased serum alkaline phosphatase, increased serum bilirubin, increased serum creatinine, increased serum transaminases, insomnia, interstitial nephritis, irritable bowel syndrome, jaundice, leg pain, leukocytosis, leukopenia, malaise, microscopic colitis, microscopic pyuria, mucosal atrophy (tongue), muscle cramps, myalgia, myasthenia, nervousness, neutropenia, ocular irritation, optic atrophy, optic neuritis, optic neuropathy (anterior ischemic), osteoporosis-related fracture, pain, palpitation, pancreatitis, pancytopenia, paresthesia, peripheral edema, petechiae, photophobia, pneumonia, proteinuria, pruritus, psychiatric disturbance, purpura, sleep disturbance, sore throat, Stevens-Johnson syndrome, stomatitis, tachycardia, testicular pain, thrombocytopenia, toxic epidermal necrolysis, tremor, urinary tract infection, urticaria, weight gain, xeroderma, xerophthalmia, xerostomia. Treatment: Discontinue medication.
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	Discontinue medication.
Contraindications and Interactions, If Known:	Hypersensitivity to omeprazole or its components.
Investigators Authorized to Prescribe:	Principal investigator and all associate investigators.

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

N/A. This study meets exemption criteria under 312.2b.1 under 21 CFR 312 and is not subject to FDA reporting requirements.

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

- ○ Registration is not required
- ◉ Registration pending
- ○ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

- ○ Registration is not required
- ○ Registration pending
- ○ Registration complete

20.0 References and Glossary

20.1 References:

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20.2 Abbreviations and Acronyms:

AHLTA - Armed Forces Health Longitudinal Technology Application
CHCS - Composite Health Care System
DEERS – Defense Enrollment Eligibility Reporting System
EEsAI - Eosinophilic Esophagitis Symptom Activity Index
EGD - Esophagogastroduodenoscopy
EoE - Eosinophilic Esophagitis
Eos/hpf - Eosinophils per high power field
EREFS - Endoscopic Reference Score
GERD - Gastroesophageal Reflux Disease
GI – Gastroenterology
HIPAA - Health Insurance Portability and Accountability Act
HPF - high power field
MHS – Military Health System
PedsQL - Pediatric Quality of Life Inventory
PHI – Protected Health Information
PI - Primary Investigator
PII – Personally Identifiable Information
PPI – Proton Pump Inhibitor
PPI-REE - PPI-responsive esophageal eosinophilia
WRNMMC - Walter Reed National Military Medical Center