**WALTER REED NATIONAL MILITARY MEDICAL CENTER**
**CONSENT TO PARTICIPATE IN RESEARCH**

**1. PROTOCOL TITLE: Randomized Controlled Trial Comparing Fluticasone plus Omeprazole with Fluticasone alone in Eosinophilic Esophagitis**

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

You may be eligible to take part in this research study. This form gives you important information about the study.

Please take time to review this information carefully. You should talk to the researchers about the research study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or your personal physician) about your participation in this study. If you decide to take part in this research study, you will be asked to sign this document. Before you sign this document, be sure you understand what the research study is about, including the risks and possible benefits to you.

Please tell these researchers if you are taking part in another research study.

You do not have to take part if you do not want to. You may also leave the research study at any time. If you choose not to take part in this research study or if you leave the study before it is finished, there will be no penalty.

Your decision will not affect your future care at Walter Reed National Military Medical Center (WRNMMC).

## 2.WHAT IS THE PURPOSE AND DURATION OF THIS RESEARCH AND WHO WILL TAKE PART?

You are being asked to take part in this research study because you have a diagnosis of Eosinophilic Esophagitis and receive care at Walter Reed National Military Medical Center. The purpose of this research study is to learn about how Eosinophilic Esophagitis (EoE) responds to treatment. Studies have shown that EoE can be successfully treated in 65% of people with a topical (swallowed) steroid, fluticasone. A stomach acid blocking medication, omeprazole, has also been shown to treat EoE in some patients. While fluticasone and omeprazole are usually used separately to treat EoE, some providers will use them both in combination. No studies have been done however to see if there is a benefit to using the medications together in the treatment of EoE. This study would help define if there is any benefit to treating EoE with both fluticasone and omeprazole, instead of fluticasone alone.

The duration of this study is 8 weeks. During this time you will be asked to visit the clinic 2 times. Today is the first visit, to provide consent to participate in the study. And complete a study questionnaire. The second visit will be to complete the follow up questionnaire and repeat the EGD procedure to monitor response to therapy. That visit will take approximately 2-3 hours. It should take approximately 10 minutes to complete the questionnaire. Additionally, you will be contacted once by phone at 4 weeks after starting therapy. This phone call is expected to take no longer than a few minutes.

There will be about 100 people taking part in the study at Walter Reed National Military Medical Center, over a period of 4 years.

This research study involves the use of Omeprazole and Fluticasone as investigational study drugs. This means that they have not yet been approved or cleared by the Food & Drug Administration (FDA) specifically for the treatment of eosinophilic esophagitis (EoE). Both drugs are FDA approved for the treatment of other medical conditions, but not EoE. Despite not being FDA approved specifically for the treatment of EoE, both of these medications are among the most commonly used medications by experts who study and treat EoE.

## 3.WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH?

You will undergo the following procedures:

1. The images from your initial Esophagogastroduodenoscopy (EGD) willbe looked at by investigators and scored for later comparison after intervention.
2. The biopsies taken at the initial EGD will be evaluated by pathologists to look for markers of eosinophilic esophagitis. They will count the number of eosinophils in the biopsy tissue and use a special stain to look for a marker called eotaxin-3 that is associated with EoE.
3. You will complete a questionnaire that quantifies your symptoms of EoE.
4. You will then be randomly assigned to one of two groups: the intervention group, or the standard group.
5. Each group will be treated for 8 weeks as a part of thisstudy.
6. You will be contacted by phone after 4 weeks of intervention and asked how many pills you have remaining and the number on the fluticasone counter.
7. At the end of 8 weeks of intervention, participants will undergo a repeat EGD to determine the effectiveness of the intervention. This is the standard of care for any patients beginning treatment for EoE. Pathologists will then evaluate the biopsies for the same tissue markers they did after the initial EGD.
8. You will again complete a questionnaire that assesses your symptoms of EoE.

| | Standard of Care | Research Protocol |
|---|---|---|
| Diagnosis of EoE made with biopsies while taking acid suppression medication | X | X |
| Special staining of esophageal tissue to look for inflammation/injury (before intervention) | | X |
| Visit to discuss options and start medications (before intervention) | X | X |
| Answer patient symptom survey | | X |
| Phone call at 4 weeks into medication intervention | | X |
| EGD performed 8 weeks after starting medication to monitor response to intervention | X | X |
| Special staining of esophageal tissue to look for inflammation/injury (after intervention) | | X |
| Answer patient symptom survey (after intervention) | | X |

Any of your samples which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, WRNMMC and/or others. However, donors of samples do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

The tissue used for this study will be kept for 10 years, in accordance with standard practices of Walter Reed National Military Medical Center.

If you will need a procedure requiring additional informed consent, a separate consent form will be given to you before that procedure.

You will be randomly assigned to one of two groups. Randomization is a process like flipping a coin and means you will have a chance of being assigned to either of the groups.

1. The ***intervention treatment group*** will take one 40mg omeprazole capsule by mouth twice daily and puff and swallow 880mcg (4 puffs of 220mcg/puff) of fluticasone twice daily.

2. The ***standard treatment group*** will take one placebo capsule by mouth twice daily and puff and swallow 880mcg of fluticasone twice daily.

3. The dosing of fluticasone will vary for children under 18 years old.

| Age | Fluticasone dose | Frequency |
|---|---|---|
| 6-11 y | 2 puff of 220mcg/puff | Twice daily |
| 12-17 y | 3 puffs of 220mcg/puff | Twice daily |

4. The dosing of omeprazole will also vary for children. The pediatric dose for omeprazole will be approximately 2mg/kg/day divided twice daily, with a max dose of 40mg per day.

| Weight | Omeprazole dose | Frequency |
|---|---|---|
| 10-20 kg | 20 mg tablet | Once daily |
| ≥20 kg | 20 mg tablet | Twice daily |

a. Your fluticasone dose will be___puffs 440mcg swallowed ____times per day.
b. Your omeprazole dose will be___capsule(s) once/twice per day.

You will have a 50% chance of being in the standard intervention (placebo) group. A placebo is an inactive, harmless substance, like a sugar pill, that looks like the study medications.

This study is a "double blind study", which means that neither you nor your study investigator will know whether you are receiving the study medication or a placebo. In the event of an emergency, there is a way to determine which you are receiving.

## WHAT ARE THE RISKS OR DISCOMFORTS FROM BEING IN THIS RESEARCH?

A) If you choose to take part in this study, there is a risk of side effects to the study drugs:

*SWALLOWED AEROSOLIZED FLUTICASONE*

Fluticasone is an inhaled steroid used in the treatment of many conditions, including asthma and allergic conditions. It is commonly used to treat eosinophilic esophagitis, but instead of being inhaled it is swallowed. For the purposes of this study, you will be taking this medication every day for 8 weeks.

Every medication has possible side effects. Although rare, you need to be aware of the possible side effects of using this medication. Listed below are some of the more commonly reported side effects.

For gastrointestinal complaints, some develop fungal infections of the mouth (≤31%).
For neurologic complaints, some experience fatigue (≤16%) or headache (2 to 14%).
For muscular complaints, some experience limb pain (2 to 12%) or joint pain (≤17%).
For respiratory complaints, some experience sinus infections (≤33%), cold symptoms (2 to 31%), or nasal congestion (3 to 16%).

*ORAL OMEPRAZOLE*

Omeprazole is an acid blocking medication that is used as a standard therapy to treat gastroesophageal reflux (GER) and is recommended by adult and pediatric gastroenterology consensus guidelines to be used to rule out GER as a cause of increased esophageal eosinophilia. Listed below are some of the more commonly reported side effects.

For gastrointestinal complaints, some experience nausea (4%), vomiting (3%), abdominal pain (5%), diarrhea (4%), constipation (2%), or regurgitation (2%).
For neurologic complaints, some experience headache (7%), dizziness (2%), back pain (1%) or weakness (1%).
For skin complaints, some experience rash (2%).
For respiratory complaints, some experience upper respiratory infections (2%) or other cough (1%).

B) In addition to the above mentioned medication risks, there are also risks associated with sedated procedures. When diagnosed with EoE, patients typically undergo multiple EGDs in order to measure response to therapies. The risks for the procedure include bleeding, pain, infection, and rarely intestinal perforation (1 in 5,000 cases). There are further risks associated with anesthesia to include nausea, vomiting, dizziness, or temporary confusion. Participants will have an EGD performed 8 weeks after starting their medication intervention. The participant will undergo cardiorespiratory monitoring throughout the endoscopic procedure, and will also have pre procedure and post procedure monitoring based on the hospital protocol.

C) Additionally, there may be psychological risks that result from participating in the research. This a placebo-controlled trial, meaning there is a 50% chance that you may be assigned to a group that will receive a placebo. A placebo is a capsule or tablet that is made to look like the treatment, but does not actually contain any medication, only sugar. All study participants will be treated with fluticasone, which is the standard therapy for EoE, half of the participants will be treated with fluticasone and omeprazole; the other half will be treated with fluticasone and a placebo. Neither you nor your doctor will know if you are receiving the actual medication or a placebo. The thought of not knowing can be stressful for some people, and should be considered before agreeing to participate in this study.

D) Every effort is made to protect your privacy and confidentiality. Study investigators will only collect the minimum amount of protected health information that is needed to carry out the study. Although efforts are made to protect your research study records, there is always a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.

E) If you are a FEMALE ABLE TO BECOME PREGNANT and you want to take part in this study, you should know that omeprazole and/or fluticasone might be harmful to (1) an unborn child if you are pregnant; or (2) an infant if you are breast-feeding. You will take a pregnancy test before you can participate in this study. You should not get pregnant or breastfeed while in this study. The only completely reliable methods of birth control are not having sex or surgical removal of the uterus. Other methods, such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy. If you become pregnant or feel you might be pregnant, contact your personal physician and the principal investigator of this study listed in the Contact Information section at the end of this document. There may also be other risks of taking part in this study that we do not yet know about.

## 5. WHAT ARE THE POSSIBLE BENEFITS FROM THISRESEARCH?

We hope that participants in this research study benefit from starting medication intervention for their EoE, which can relieve often painful symptoms. Whether or not the patient decides to participate in this study, they will have close follow up and monitoring with their Gastroenterologist. This study offers one additional point of contact with a Gastroenterologist in the form of a phone call at 4 weeks after starting the medication intervention. This phone call will serve to assess the patient's ability to take the medication and any side effects they may be experiencing. However, there is no guarantee that the participant will benefit from being in this study.

## 6. WHAT ARE THE ALTERNATIVES TO TAKING PART IN THISRESEARCH?

There may be other options for treating eosinophilic esophagitis. Alternative treatments and/or procedures that may be available to you include: swallowed budesonide, avoidance of food allergens. You should talk with your personal physician (if applicable) about these options.

Choosing not to take part in this research study is also an option.

The medications involved in this research study may also be available through your personal physician without taking part in this study.

## 7. IS THERE COMPENSATION FOR YOUR PARTICIPATION IN THIS RESEARCH?

No, you will not receive any compensation for participating in this study.

## 8. ARE THERE COSTS FOR PARTICIPATING IN THISRESEARCH?

No, there are no costs to you for taking part in this research study.

## 9. WHO IS CONDUCTING THIS RESEARCH?

This research is conducted by clinical researchers within the Walter Reed National Military Medical Center Departments of Pediatrics, Gastroenterology, and Pathology.

## 10. STUDY SPONSOR (the organizations or persons who oversee the study and are responsible for analyzing the study data):

As the sponsor of this research, the Department of Defense may have access to your research data in accordance with DoDI 3216.02.

## 11. SOURCE OF FUNDING:

Funding has been requested from the Walter Reed Department of Research Programs funding for Graduate Medical Education Research.

## 12. PRINCIPAL INVESTIGATOR (the person(s) responsible for the scientific and technical direction of the study):

Steve B. Min, MD LTC, MC
Pediatric Gastroenterology Service, Department of Pediatrics
Walter Reed National Military Medical Center
Office: 301-295-4959
steve.b.min.mil@mail.mil
Walter Reed National Military Medical Center
Department of Health Services

## 13. LOCATION OF THE RESEARCH:

Gastroenterology Service, Department of Pediatrics at the Walter Reed National Military Medical Center in Bethesda, MD

## 14. DISCLOSURE OF FINANCIAL INTERESTS AND OTHER PERSONAL ARRANGEMENTS:

Neither the Principal Investigator, research team members or their immediate family members, nor Walter Reed National Military Medical Center have any financial interests or other personal arrangements with the study drug manufacturers and receive no compensation for performing this study.

## 15. WHO WILL SEE MY INFORMATION (PRIVACY) AND HOW WILL IT BE PROTECTED (CONFIDENTIALITY)?

Records of your participation in this research study may only be disclosed in accordance with state and federal law, including the Federal Privacy Act, 5 U.S.C.552a, and its implementing regulations. DD Form 2005, Privacy Act Statement - Military Health Records, contains the Privacy Act Statement for the records. A copy of DD Form 2005 can be given to you upon request, or you can read on-line at: http://www.dtic.mil/whs/directives/infomgt/forms/eforms/dd2005.pdf.

Procedures to protect the confidentiality of the data in this study include but are not limited to: All hard copies of data will be kept in a locked file cabinet in the securable 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 assigned by the PI, and the file linking the subject's identity with a numeric code will be stored electronically on the PI's password protected computer.

Researchers will make every effort to protect your privacy and confidentiality; however, there are risks of breach of information security and information loss.

If applicable, a description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This web site will not include information that can identify you. At most, the Web site will include a summary of results. You can search this Web site at any time.

By signing this document, you give your permission for information gained from your participation in this research study to be published in literature, discussed for educational purposes, and used generally to further science. You will not be personally identified; all information will be presented as anonymous data.

Complete confidentiality cannot be promised for military personnel, because information regarding your health may be required to be reported to appropriate medical or command authorities to ensure the proper execution of the military mission, including evaluation of fitness for duty.

The principal investigator and the associate investigators will have access to your records and agree to safeguard your protected health information by using and disclosing it only as permitted by you in this consent or as directed by state and federal law.

## 17. LONG TERM USE OF DATA

The investigator has requested to save selected data collected from your participation in this research study for possible use in future research. You have a number of options with regard to this request. If the stored data has an identifying link you can request to be contacted and sign a separate consent form to allow the use or available of this data in another study. You may also choose either to not allow any further use of your data or give consent now for the use your data to be used in future studies. This future research may be in the same area as the original study or it may be for a different kind of study.

Any future research using your retained data will require a research protocol for the proposed study approved by an Institutional Review Board (IRB) (a committee responsible for protecting research participants) or other authorized official responsible for protecting human subjects of research. The data protections for privacy and confidentiality described in this consent form will apply to any future use of your stored data.

## 18. WHAT HAPPENS IF YOU ARE INJURED AS A RESULT OF THIS RESEARCH?

If you think that you have a research-related injury, notify your Principal Investigator immediately at 301-295-4959.

If you are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., active duty military, dependent of active duty military, retiree),

you are authorized space-available medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at DoD hospitals or DoD clinics.

For DoD healthcare beneficiaries, transportation to and from hospitals or clinics will not be provided or paid for by DoD. Unless you are covered by TRICARE, no DoD reimbursement is available if you incur medical expenses to treat research- related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights.

## 19. WHAT WILL HAPPEN TO YOUR SAMPLES AFTER THIS RESEARCH HAS ENDED?

During this research study, you could be asked to provide the following types of samples (biological specimens): Gastrointestinal mucosal biopsies obtained from Esophagogastroduodenoscopy.

Although research that uses your samples may lead to the development of new inventions, products, or discoveries (some that might be patented and licensed), there are no plans to pay you for them.

While this study is on-going, your samples will be handled in accordance with this study's protocol and applicable regulations at the Pathology Lab at Walter Reed National Military Medical Center.

When this study is over, your samples will be kept at the Walter Reed National Military Medical Center pathology laboratory in accordance with standard operating procedures for any patient tissue sample, currently 10 years. At the completion of the 10 year time period, specimens will be destroyed.

## 20. WHAT HAPPENS IF I WITHDRAW FROM THIS RESEARCH?

You may withdraw your consent at any time and stop participating in this research study without affecting your eligibility for care or any other benefits to which you are entitled. Should you choose to withdraw, you must tell the study investigator as soon as possible. By leaving this study at any time, you in no way risk losing your right to medical care and there will be no penalty to you and you will not lose any of your benefits to which you are otherwise entitled.

Should you choose to withdraw, you must notify the primary investigator and return all study medication to the pharmacy which dispensed the medication. Your condition

will continue to be treated in accordance with acceptable standards of medical treatment.

If you do not follow these procedures, you may experience a recurrence of your previous eosinophilic esophagitis symptoms.

If you are receiving treatment as part of this research study, you will no longer be eligible for such research-related treatment. Contact your personal physician to discuss medical treatment for your condition.

Please note that withdrawing your consent to participate in this research does not fully revoke your HIPAA Authorization Form to use/disclose your protected health information. To make that revocation, please send a letter to the principal investigator as discussed in the HIPAA Authorization Form.

The principal investigator of this research study may terminate your participation in this research study at any time if he determines this to be in your best interest, if you are unable to comply with the procedures required, or if you no longer meet eligibility criteria.

## 21. VOLUNTARY PARTICIPATION:

The decision to take part in this research study is completely voluntary on your part. You will be informed if significant new findings develop during the course of this research study that may relate to your decision to continue participation.

## 22. INCIDENTAL FINDINGS

There is a possibility that while reviewing your test results we may see an abnormality that we did not expect to see in this study. This is what is called an "incidental finding."

We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by phone. In the case of a potential serious emergency, the researcher will inform you right away.

You do not have an option to decline receiving information about an incidental finding. A qualified person (usually a member of the research team) will talk to you if there is an incidental finding.

We will also give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

- An incidental finding may cause you to feel anxious
- Since an incidental finding will be part of your medical record, you could face greater difficulty in getting health or life insurance

The costs for any care that will be needed to diagnose or treat an incidental finding would

not be paid for by this research study. These costs would be your responsibility. If you are a DoD beneficiary, you will have access to care through standard Military Health System and TRICARE procedures.

## 23. CONTACT INFORMATION:

**Principal Investigator (PI)**

The Principal Investigator or a member of the research staff will be available to answer any questions throughout this study.

Principal Investigator: Steve B. Min, MD LTC, MC
Phone: 301-295-4959
Mailing Address: Walter Reed National Military Medical Center
Department of Pediatrics
8901 Wisconsin Avenue
Bethesda, MD 20889

**Institutional Review Board (IRB) Office**

If you have any questions about your rights as a research participant or if you have concerns or complaints about the research study, please contact the Human Protections Administrator, WRNMMC Department of Research Programs in Building 17 at #301-295-8273 or WRNMMC Staff Judge Advocate Office at 301-295-2215.

IF THERE IS ANY PORTION OF THIS DOCUMENT THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING. YOU MAY CONSULT WITH YOUR PERSONAL PHYSICIAN OR LEGAL ADVISOR, IF YOU WISH.

A signed and dated copy of this document will be given to you.

**SIGNATURE OF PARTICIPANT**

| | |
|---|---|
| Printed Name of Participant | Time |
| Signature of Participant | Date |

**SIGNATURE OF INDIVIDUAL ADMINISTERING CONSENT**
(Can only be signed by an investigator or staff approved to administer consent)

| | |
|---|---|
| Printed Name of Administering Individual | Time |
| Signature of Administering Individual | Date |

## 24. WHAT IF THIS STUDY INVOLVES YOUR CHILD OR DEPENDENT?

This study involves minor children/dependents, with an age range of 6-17 years.

A separate assent of the child is required with the signature of the parent or guardian and the investigator.

At times there may be inconsistency between the permission of the parent and the assent of the child. A rule of thumb is: a "no" from a child overrides a "yes" from the parent, but a "yes" from a child does not override a "no" from a parent.

**SIGNATURE OF PARENT OR GUARDIAN**

| | |
|---|---|
| Printed Name of Parent or Guardian | Time |
| Signature of Parent or Guardian | Date |
| Printed Name of Parent or Guardian | Time |
| Signature of Parent or Guardian | Date |

**SIGNATURE OF INDIVIDUAL ADMINISTERING CONSENT**
(Can only be signed by an investigator or staff approved to administer consent)

| | |
|---|---|
| Printed Name of Administering Individual | Time |
| Signature of Administering Individual | Date |