IDCRP-115: A randomized controlled trial evaluating single-dose rifaximin versus azithromycin with loperamide adjunct for treatment of acute watery diarrhea (TrEAT TD 2.0)

NCT05677282

Informed Consent

USUHS IRB Approval Date: 03/11/2025

CONSENT TO PARTICIPATE IN RESEARCH and AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH (HIPAA)

Research Study: A Randomized Controlled Trial Evaluating Single-Dose Rifaximin versus Azithromycin with Loperamide Adjunct for Treatment of Acute Watery Diarrhea (TrEAT TD 2.0)

You may be eligible to participate in this research study. This form gives you important information about the study so you can make an informed decision on whether you decide to participate. Please take time to carefully review this information. You should talk to the researchers about the research study and ask them any questions you may have. You may also wish to talk to others (for example, your friends, family, or personal physician) about your participation. You do not have to take part in this study. Participation is voluntary. You may also leave the research study at any time without any impact on your future care. 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 in all sections of this form, including possible risks and benefits.

1. BACKGROUND

Traveler's Diarrhea (TD) is a common problem during overseas travel in both military servicemembers and civilians, particularly when visiting less developed countries. TD is an infection usually acquired after exposure to contaminated food or beverages. Most TD is caused by bacteria which is why when the illness is more severe it is treated with an antibiotic.

In addition to the immediate health impact of diarrhea, TD may lead to decreased job performance, missed duty days, and other health problems. Because TD occurs commonly in deployed military and may impact operational readiness, optimizing most effective treatment is a priority for Force Health Protection.

When TD is more severe and affects the person's ability to perform their daily activities the current recommendations are to treat with a combination of an antibiotic and an over-the-counter drug called loperamide (brand name Imodium). Loperamide is used to help slow the action of the intestine, called antimotility agents, which can make a person feel better, but it does not cure the infection. In the more severe TD illness, the antibiotic is used to clear (or cure) the infection. Several studies have shown that for moderate to severe TD a combination of loperamide and antibiotics is the best way to manage diarrhea. Azithromycin (an antibiotic given as a single pill only once) plus loperamide is the current recommended treatment for moderate to severe TD. Azithromycin, similar to other antibiotics, has potential for side effects as well as becoming less effective if bacteria develop resistance. Because of this it is important to evaluate other antibiotics to provide safe and effective alternative treatment.

A different antibiotic called rifaximin has been shown in several prior studies to also be effective for treating TD both when given over 5 days or as a single high dose (also with loperamide). Rifaximin is absorbed from the gut at extremely low levels, so it stays in the intestine and has been shown to be very safe.

2. KEY INFORMATION

The purpose of this study is to compare a lower single dose, more commonly used in clinical practice, with loperamide to the current standard approach of single dose azithromycin with loperamide. The expected overall duration of the research study enrollment will be 3 years in a total of 150 US and UK military servicemembers. Your participation in this study will last up to 3 months (follow-up out to 21 days in country plus a 3-month follow-up brief electronic questionnaire). More details are provided in the following pages including discussion of benefits and risk (page 3). Primarily risks include possible gastrointestinal side effects from the study drugs and bruising or soreness from blood draw. A possible risk is that rifaximin will be inferior and your clinical cure will be delayed.

3. WHO IS ELIGIBLE TO PARTICIPATE?

This study is available to active duty military personnel deployed to Kenya (UK military) or Honduras or Djibouti or the Philippines (US military). You are being asked to consider participation in this research study because you have diarrhea that started less than 4 days ago. Your doctor has determined that you do not require being put in the hospital to treat your diarrhea. If there is visible blood in your diarrhea and/or you have a fever you are not eligible

to participate. After you agree to participate, the doctor will ask questions to determine if your diarrheal illness meets criteria to require antibiotics as well as take a medical history and examine you to be sure you are treated appropriately and are eligible to proceed with the study. If the study investigator has safety concerns regarding your study participation, such as current or past liver disease or use of medications that may interact with the study treatment, you will not be eligible to participate.

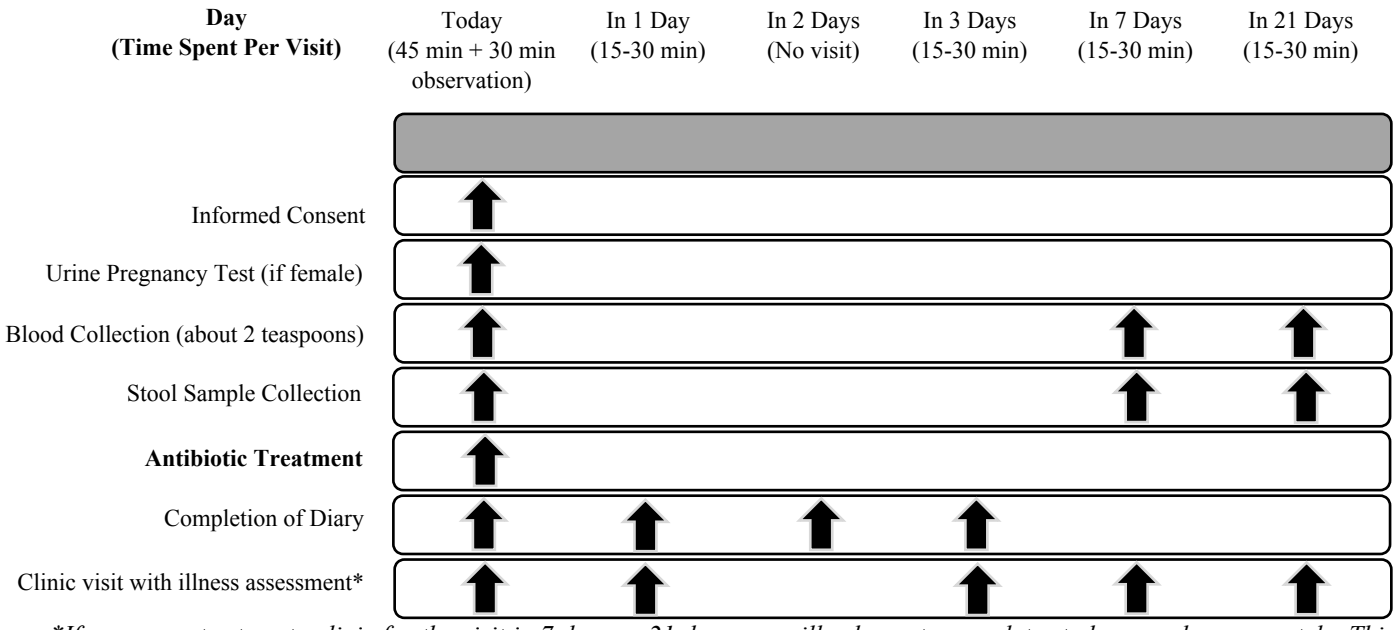
4. WHAT ARE THE STUDY PROCEDURES?

Summary: The study requires 1) taking a single dose antibiotic plus loperamide to treat your TD given today with a 30 min observation period after taking the study medication, 2) providing blood and stool samples at different time points to evaluate your infection and your body's immune response, 3) completing a daily symptom diary following treatment, 4) being seen by the study doctor to monitor your illness and recovery, and 5) complete a brief electronic questionnaire at 3 months.

You will be randomly assigned to one of the two treatment groups. Randomization is a process like flipping a coin and means you will have a 50% chance of being assigned to either group. The two groups are 1) rifaximin 550 mg as a single dose with loperamide 4 mg initially followed by 2 mg after each unformed stool or 2) azithromycin 500 mg as a single dose with loperamide 4 mg initially followed by 2 mg after each unformed stool. Whichever group you are randomized to, you will take the antibiotic dose and 4 mg of loperamide.

This is a double-blind research study, which means that neither you nor the research team will know which antibiotic you received. In the event of an emergency, there is a way to find out which one you received.

Your participation in this study will involve the following:



**If you cannot return to clinic for the visit in 7 days or 21 days, we will ask you to complete study procedures remotely. This includes self-collecting a small stool sample in an OMNIgene tube, a stool smear on a filter paper card, and a few drops of blood using a finger-stick device similar to blood sugar monitoring used by diabetic people. For remote visits in 21 days, we will also contact you to check how you are doing and if there are any changes to your medications. All supplies for self-collected samples will be provided. Self-collected samples will be stored at room temperature until you can give them to the site study staff or mail them to the lab using the provided pre-paid shipping materials.*

In addition to the procedures above, 3-months after enrollment you will be asked to complete an online questionnaire. Some travel-associated illnesses can persist or show up after the initial diarrheal illness. The questionnaire you will be asked to complete will assess the existence of functional bowel disorders, such as post-infectious irritable bowel syndrome (PI-IBS). The questionnaire will take approximately 10 minutes to complete. You will be asked to provide your email address and/or cell phone number to receive the questionnaire

electronically. Finally, by agreeing to participate in this research study, you allow the researchers to collect information about your pre-travel/deployment health risks and post-travel/deployment related illnesses for up to 1 year through the military's electronic medical record. The research results about you will not be shared with you.

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

The study is being done to evaluate if rifaximin compares favorably to azithromycin in TD treatment. A possible risk is that rifaximin will be inferior and your clinical cure will be delayed. The study doctor will be monitoring you closely to determine if additional treatment is required. **If your illness is becoming more severe, please return to the clinic and/or contact the study investigator using the study clinic phone number listed on your study contact card.**

Other risks are related to antibiotic potential side effects and bruising or soreness at the site of the blood draw. The side effects associated with the antibiotics are uncommon, occurring in less than 5% of patients. Of the possible side-effects, more common ones include rash, nausea, vomiting, stomachache, headache, gas, diarrhea/loose stools, feeling a constant urge to have a bowel movement even though your bowel may be empty, an urgent need to have a bowel movement, indigestion and vaginal yeast infection. Allergies to these medications are rare, occurring in less than 1% of patients. The study antibiotics used in this research study might be harmful to an unborn child. Therefore, if you are a FEMALE of CHILD-BEARING POTENTIAL, you may not be pregnant and participate. You must take a pregnancy test before you take part in this study. Constipation and abdominal cramping are potential side effect of loperamide use.

You may experience discomfort, bleeding, bruising, soreness, swelling, light-headedness, and in rare cases, fainting or infection at the site where blood is drawn. Any adverse event you experience during the study period should be reported to the investigator at each follow-up visit unless you are so unwell you consider the need for urgent attention. In this case you should report to the urgent medical care facility and inform them you are part of the study. Data security is used to protect and limit use of your personal information in research study records; however, there is potential risk of breach of your personal information in your medical records or other information researchers have stored about you.

6. WHAT ARE THE POSSIBLE BENEFITS FROM THIS RESEARCH?

Rifaximin, as a nonabsorbable antibiotic, has a better safety profile than azithromycin and promising clinical results on treating TD. Therefore, one potential benefit is a safer effective TD treatment. In addition, all research participants will be closely monitored beyond what is done in standard clinical practice providing for timely care as needed. From the standpoint of the US military, this research has the potential to optimize deployment-related clinical practice guidelines in support of Force Health Protection.

7. WHAT ARE THE ALTERNATIVES TO TAKING PART IN THIS RESEARCH?

You will receive standard medical treatment that may or may not include the treatment that is part of the planned research study depending on the assessment of your treating doctor. Choosing not to participate in this research study is your alternative to volunteering for the research study.

8. IS THERE COMPENSATION FOR YOUR PARTICIPATION IN THIS RESEARCH?

Yes, you will receive a maximum of $250.00, administered in the form of Amazon gift codes. You will receive $50.00 compensation for each completion of blood collection Today (enrollment), in 7 days, and in 21 days. Compensation will be the same, whether blood collection is done in-person or remotely as part of a virtual visit. You will receive $25.00 compensation for each completed clinical follow up visit on Days 1 and 3. You will receive $50.00 compensation after completion of the 3-month questionnaire if completed off duty for US servicemembers.

Under 24 USC 30, payment to Federal Employees and Active Duty military personnel for participation in research while on duty is limited to blood donation. They may not receive any payment or non-monetary compensation for

participation in a research study unless they are off duty or on leave during the time they are participating in the protocol. There are no restrictions on payment while off-duty.

9. ARE THERE COSTS FOR PARTICIPATING IN THIS RESEARCH? NO

10. STUDY SPONSOR (organization/persons who oversee the study):

The study is being conducted by the Infectious Disease Clinical Research Program (IDCRP) of the Uniformed Services University. The IDCRP is overseeing the study and is responsible for analyzing study data. The Department of Defense may have access to your research data in accordance with DoDI 3216.02.

11. SOURCE OF FUNDING: Defense Health Program (US Department of Defense)

12. LOCATION OF THE RESEARCH:

The research will be conducted at Joint Task Force Bravo, Soto Cano Air Base, Honduras; at Camp Lemonnier, Djibouti (CLDJ); and at Fort Magsaysay for US servicemembers and at the British Army Training Unit, Kenya for UK servicemembers.

13. DISCLOSURE OF FINANCIAL INTERESTS AND OTHER PERSONAL ARRANGEMENTS:

There are no financial interests or other personnel arrangements to disclose.

14. 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: https://www.esd.whs.mil/Portals/54/Documents/DD/forms/dd/dd2005.pdf.

The research team will keep your research records. These records may be looked at by staff from the Institutional Review Board (IRB) and the DoD Higher Level Review as part of their duties. These duties include making sure that the research participants are protected. Confidentiality of your records will be protected to the extent possible under existing regulations and laws but cannot be 100% guaranteed. Procedures to protect the confidentiality of the data in this study include but are not limited to: use of coded data, computer password protection, and locking of drawers and offices. Researchers will make every effort to protect your privacy and confidentiality; however, there are small risks of breach of information security and information loss.

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. 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. Information gained from your participation in this research study may be published in literature, discussed for educational purposes, and used generally to further science. You will not be personally identified when your information is shared in these ways; all information will de-identified.

15. 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. Your participant ID, which is assigned at enrollment, is considered an identifier and may be used or shared for future research. You may choose either to not allow any further use of your data or give consent for the use of your data to be used in future studies. This future research would be in the same area as the original study. You will be provided choices at the end of this consent form to allow or deny use in future research studies.

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 participants of research. The data protections for privacy and confidentiality described in this consent form will apply to any future use of your stored data. Identifiable information may be removed from your data or specimens and after such removal the data or specimens may be used or shared for future research without addition consent from you.

Future use of Biologic Specimens: The investigators in this study are requesting your permission to store your samples for future use in other research studies. The specifics of these future research studies are unknown currently, but these studies most frequently focus on diarrheal disease.

Future research investigators requesting portions of your samples must have the approval of the Principal Investigator and must have a research protocol for their newly proposed research study approved by an Institutional Review Board (IRB) (a committee responsible for protecting research participants). It is possible these other researchers will request approval from an IRB to contact you in the future.

Potential risk would occur if the confidentiality of your data is breached. Because of the consequences of a breach of confidentiality, every effort will be made by the bank to protect your privacy. The storage bank's procedures to protect the confidentiality of your data include coded data, computer password protection, creation of firewalls around data, and locked laboratory space. A firewall is a protection or barrier within a computer to protect the information from being viewed by unauthorized people.

Your samples could be stored indefinitely at the bank, or until none is left to use. Generally, you will not be provided with the results of the future studies using your samples from this bank. This is typically the case because the research results at that early point will not have a clear meaning for or direct clinical benefit to you. You may request that your specimen be withdrawn from the bank at any time if you decide you no longer want to participate. This can be done by notifying the Principal Investigator (PI) as listed at the end of this document.

16. INCIDENTAL FINDINGS

Due to the nature of the type of data that will be collected and specimen testing that will be completed, we do not anticipate any incidental or unexpected findings that would impact participants.

17. VOLUNTARY PARTICIPATION

The decision to take part in this research study is completely voluntary on your part, which means 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 or loss of benefits to which you are otherwise entitled. 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.

18. WHAT HAPPENS IF I WITHDRAW FROM THIS RESEARCH?

Should you choose to withdraw, you must contact the Principal Investigator and/or study personnel at the site where you enrolled. If you decide to no longer participate in this research study, the researcher will keep your data and specimens that were collected during this research study and collect any unused research products from you.

The Principal Investigator of this research study may terminate your participation 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. The sponsor of this research study may terminate the research study and/or your participation in this research study for safety reasons.

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

There are small risks associated with the blood draw: pain/discomfort, swelling, bruising, lightheaded feeling, and fainting/passing out. There is a small risk associated with receiving the study medications as previously described.

The research staff are trained to assess and address the problem in accordance with clinical care guidelines. A physician will be available at each site to monitor any adverse events. Medical care for any research related injuries will be provided to participants through the Military Health Care.

20. AUTHORIZATION TO USE AND/OR DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH (HIPAA):

Purpose of Authorization -- An Authorization is your permission to use or disclose (release) your health information. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, as implemented by the Department of Defense (DoD), requires that an Authorization contain certain core elements and required statements.

Authorization -- The disclosure of your protected health information is necessary in order to be able to conduct the research project described. The demographic information will help us understand if effectiveness of any of the study products varies between groups of people. The information on your history of medical conditions will help us to understand if/how the study products provide a benefit for long term stomach and joint problems.

Records of your participation in this study may only be disclosed in accordance with state and federal law, including the Privacy Act (5 U.S.C. 552a) and the Health Insurance Portability and Accountability Act of 1996 and its implementing regulations (45 CFR 160 & 164). You have the right to revoke your authorization at any time, please notify the study Principal Investigator in writing if your wish to revoke your authorization. Note: Protected health information of military service members may be used or disclosed for activities deemed necessary by appropriate military command authorities to ensure the proper execution of the military mission.

(a) What health information will be used or disclosed (released) about you? The identifiers and/or personal health information collected, used, or disclosed includes Name, Address, Age, Phone Numbers, Email Addresses, cell phone number, health information including medication prescriptions, travel dates and destinations, exposures during travel, and laboratory testing results. The purpose of collecting and using this information is to provide contact information for research personnel to contact you as well as understand whether the study product you receive helps to treat TD.

(b) Who will be authorized to use or disclose (release) your health information? The study investigators may use or disclose your health information. Protected health information regarding adverse events, serious adverse events, vitals, and pregnancy test results will be gathered from any military health system, military treatment facility, and Defense Health Agency treatment centers. Military Treatment Facilities who will treat you over the next 5 years, and the Defense Health Agency, are permitted to make the requested use/disclosure of your PHI.

(c) Who may receive your health information?

- Uniformed Services University (USU) IRB
- Infectious Disease Clinical Research Program (IDCRP)
- State and Federal Government representatives, when required by law
- Henry M. Jackson Foundation for the Advancement of Military Medicine or their representatives
- Naval Medical Research Center (NMRC)
- US Naval Medical Research Unit-SOUTH (NAMRU-SOUTH) - Research Laboratory
- US Naval Medical Research Unit- (NAMRU-EURAFCENT) - Research Laboratory
- Joint Task Force- Bravo, Soto Cano Air Base, Honduras
- Camp Lemonnier, Djibouti (CLDJ)
- United Kingdom Ministry of Defence - Regulatory Authority for the United Kingdom

You need to be aware that some parties receiving your protected health information may not have the same obligations to protect your protected health information and may re-disclose your protected health information to parties not named here. If your protected health information is redisclosed, it may no longer be protected by state or federal privacy laws.

(d) What if you decide not to sign this authorization? The MHS **will not** condition (withhold or refuse) treatment that is not part of this study, payment, enrollment, or eligibility for benefits on whether you sign this Authorization.

(e) ***Is your health information requested for future research studies?*** Yes, your health information *is* requested for use or disclosure (release) in future research studies. The specifics of these future research studies are unknown at this time, but these studies will likely address diarrheal diseases.

Your health information and stool and blood samples will not be used for future research studies unless you give your permission by **initialing** your choice below:

_____Yes, I DO give permission to use my **health information** for future research studies

_____No, I DO NOT give permission to use my **health information** for future research studies

_____Yes, I DO give permission to use my **samples** for future research studies

_____No, I DO NOT give permission to use my **samples** for future research studies

(f) ***Can you access your health information during the study?*** You may have access to your health information at any time unless your identifiers are permanently removed from the data.

(g) ***Can you revoke this authorization?***

- You may change your mind and revoke (take back) your Authorization at any time except to the extent that the MHS has already acted in reliance on your Authorization. Even if you revoke this Authorization, any person listed above who received your Authorization for purposes of the research study may still use or disclose (release) any already obtained health information as necessary to maintain the integrity or reliability of this research.
- If you revoke this Authorization, you may no longer be allowed to participate in this research study.
- If you want to revoke your Authorization, you must write to the Study Doctor/Investigator at your local site.

(h) ***Does this authorization expire?*** No, it does not expire.

(i) ***What else may you want to consider?***

- No publication or public presentation about the research described above will reveal your identity without another signed Authorization from you.
- If all information that does or can identify you is removed from your health information, the remaining deidentified information will no longer be subject to this Authorization and may be used or disclosed (released) for other purposes.

Once your health information is shared or disclosed (released) outside of the MHS, the privacy of your health information cannot be guaranteed, and it may no longer be protected by the Federal privacy laws (such as the HIPAA Privacy Rule).

21. CONTACT INFORMATION

Principal Investigator (PI) (the person(s) responsible for the scientific and technical direction of the study)

The Principal Investigator or a member of the research staff will be available to answer any questions throughout this study. Principal Investigator: Dr. David Tribble; Phone: (240) 694-2984, 6720B Rockledge Drive Suite 340, Bethesda, MD 20817

Human Research Protection Program (HRPP) Office

The HRPP Office Point of Contact and/or Human Protections Administrator (HPA) will be available to answer questions or discuss concerns you may have about this research study. Uniformed Services University; Human Protections Administrator/HRPP POC: Dr. Petrice Longenecker; Phone: (301) 295-0819

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 USU IRB Office at: Telephone Number: (301) 295-0819; 4301 Jones Bridge Road, Room A2051, Bethesda, MD 20814

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

By signing below, I agree that I have been provided time to read the information describing the research study in the consent form. The content and meaning of this information have been explained to me. I have been provided with the opportunity to ask questions. I voluntarily consent to participate in this study. By signing this form, I have not given up any of my legal rights as a research participant.

_____

Printed Name of Participant

_____ _____

Signature of Participant Date

SIGNATURE OF INDIVIDUAL ADMINISTERING CONSENT

_____

Printed Name of Administering Individual

_____ _____

Signature of Administering Individual Date