Title of research study: Physiology of GERD and Treatment Response

Investigator: Michelle Dossett, MD, PhD, MPH

California Experimental Subjects Bill of Rights

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study.
  - The procedures to be followed.
  - Any drug or device to be used.
- Any common or important discomforts and risks.
- Any benefits you might expect.
- Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study.
  - Medical treatment, if any, that is available for complications.
- Whether or not you take part is up to you.
- You can choose without force, fraud, deceit, duress, coercion, or undue influence.
- You can choose not to take part.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to take part, you will be given a signed and dated copy of this document.

Key Information about This Research Study

You are invited to participate in a research study. The purpose of this research is to better understand the relationship between gastroesophageal reflux disease (GERD) symptoms, physiology (e.g., heart rate and the amount of sweat produced by the skin), and response to treatment with amitriptyline. Amitriptyline is an FDA-approved medication for depression. In low doses, it can be helpful for treating nerve pain. You are invited to be in this study because you have GERD-related symptoms with a hypersensitive esophagus. Your participation in this research will involve 2 visits and will last about 2 months. We expect about 60 people at UC Davis will participate in this research.

Participation in this study will involve completion of questionnaires, study diaries, meeting with a healthcare provider about your symptoms, and taking a medication known as amitriptyline for 2 months. There is also an optional blood draw. All research studies involve some risk. These risks are described in detail later in this document. There is the possibility that you may benefit from participation in this study.

Here are some reasons you may not want to participate in this research:

- You will be asked to complete a daily diary of your symptoms for a few weeks.
- You will be asked to take a medication, amitriptyline 10 mg, once a day at bedtime for 2 months. Some individuals experience side effects with this medication which will be discussed later in this consent.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. There may be other choices available to you. Some other choices may include talking with your gastroenterologist or primary care physician about other medications for your symptoms. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions you need to help decide whether or not to join this study.

Information to help you understand research is online at
http://www.research.ucdavis.edu/policiescompliance/irb-admin/for-research-participants.

What if I have Questions?

The person in charge of this study is Dr. Michelle Dossett. If you have questions or concerns about this study, please contact her at 916-734-5367.

For non-emergency issues you can call the UCDMC Hospital Operator (916-734-2011), tell the Operator you are participating in a research study and you wish to talk to the internal medicine resident on-call. In the case of an emergency, dial 911 from any phone.

If you have any questions about your rights as a research subject or have complaints about the research study or study team, you may talk to a team member at the Institutional Review Board (IRB) at (916) 703-9151, hs-irbadmin@ucdavis.edu, or 2921 Stockton Blvd, Suite 1400, Room 1429, Sacramento, CA 95817. The IRB is a group of people who oversee research.

How is this research funded?

This research is being funded by the National Institutes of Health (NIH) also called the sponsor. Sponsors may change or be added.

UC Davis is being paid to conduct this study, but the study doctor and research staff have not received any direct income from the sponsor.

Why is this research being done?

We are trying to understand if there is an association between GERD symptoms (also known as acid reflux or heartburn), a patient's physiology (their heart rate and the amount of sweat produced by the skin measured as skin conductance), and their response to treatment with amitriptyline. Amitriptyline was originally designed as an antidepressant medication. However, in much smaller doses, it functions as what we call a neuromodulator. It can help to decrease pain signals that are sent to the brain. Data suggests that this medication can be helpful in reducing GERD-related symptoms in patients with a hypersensitive esophagus. However, we cannot predict who will respond best to this medication.

We hypothesize that certain physiologic markers may help predict response to amitriptyline. To measure your physiology, we will examine markers of the stress response, also known as the "fight or flight" response. We will ask you to wear a chest strap to measure your heart rate and breathing rate and 2 electrodes on your fingers to measure your skin conductance (how well your skin conducts tiny amounts of electricity based on how much sweat your skin produces). You will only wear the monitors during

your first study visit. We will also ask you to consider providing a sample of blood so that we can analyze whether your genes or certain small molecules in the blood help to predict your response to treatment.

You may notice that the study healthcare provider (a physician or nurse practitioner) you are meeting with is also wearing electrodes on their fingers. There is some data that suggests that healthcare providers may mirror patients' physiology and we are also testing whether this is true.

What happens if I say yes, I want to be in this research?

If you decide to participate in this research study, the researchers will ask you to

Study Visit #1 (today)

- Review your medication list
- Measure your height and weight
- Provide a blood sample (optional), approximately 2 teaspoons (10 mL)
- Complete questionnaires
- Wear a chest strap to monitor your heart rate and breathing rate and 2 electrodes on your fingers to measure skin conductance. You will wear these devices during your visit with the study healthcare provider.
- Meet with a study-affiliated healthcare provider about your GERD symptoms. This visit will be video and audio recorded. Only the study team will have access to this data. During the COVID-19 pandemic, you may meet with the healthcare provider via a telehealth platform instead of in-person, and your interaction will be video and audio recorded on the telehealth platform.
- Complete additional questionnaires

Between Study Visits (2 months)

- Take the study medication (amitriptyline) daily before bed
- Complete a daily symptom diary for 2 weeks after Visit #1 and again for 2 weeks before Visit #2
- Study staff will check in with you by phone or email periodically

Study Visit #2 (in 2 months)

- Return symptom diaries
- Provide a blood sample (optional), approximately 1.5 teaspoons, (7.5 mL)
- Complete questionnaires
- Meet with a study team member
- Discuss next steps regarding medication (tapering off or continuing)

How is being in this study different from my regular health care?

If you take part in this study, the main difference between your regular care and the study is that we will give you a 2 month's supply of medication and ask you to complete symptom diaries and have your physiology measured while you meet with our study healthcare providers.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for:

- Attending 2 study visits
- Taking the study medication daily as prescribed for 2 months
- Completing study questionnaires and symptom diaries

Do I have to be in this study? What if I say "yes" now and change my mind later?

No, you do not have to be in this study. Taking part in research is voluntary. You can choose to be in the study or not be in the study. If you decide to be in the study, you can choose to leave the study at any time.

If you decide not to take part in the study, or if you choose to leave the study, your choice will not affect any treatment relationship you have with healthcare providers at UC Davis Health or any services you receive from them. No matter what you decide, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

Please let the researchers know if you choose to leave the study. We will tell you how to leave the study safely.

Instead of being in this research study, your choices may include: no medical treatment, treatment with other kinds of medications, or treatment with the medication offered in this study but without the physiologic measurements or associated study questionnaires and diary.

If you decide to leave the research, contact the study team so the investigator can work with you to create a safe plan for your withdrawal. This will include instructions for how to taper your medication to reduce the risk of side effects.

If you stop being in the research, data and specimens that have already been collected will not be removed from the study database.

What are my other choices if I do not take part in this study?

You do not have to be in this research study to get care for your GERD. If you decide not to take part in this study, you have other choices. For example:

You may decide not to get treatment.
You may choose to take another medication recommended by your physician.
You may choose to take part in a different study if one is available.
These options may have risks. Discuss the possible risks and benefits with your study doctor.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

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Can I be removed from the research without my OK?

The researchers may take you out of the study, even if you want to continue, if:

- your health changes and staying on the study is no longer in your best interest;
- you do not follow the study rules or you no longer meet the requirements to be in the study; or
- the study is stopped by the sponsor or researchers.

Is there anyway being in this study could be bad for me?

There are risks to participating in this research. The study doctor and study team will monitor you to see if you are experiencing any harm related to your participation. If you experience any pain or discomfort, you must inform the study team as soon as possible.

- Physical Risks
    - Some patients experience side effects when taking amitriptyline.
        - The most common side effects are dry mouth (up to 50%) and sleepiness (up to 50%).
        - Less common side effects include dizziness (2-15%), fatigue (up to 30%), constipation (up to 20%), headache (5%), agitation (less than 5%), tremor (up to 15%), blurred vision (up to 13%), nausea (up to 20%), insomnia (up to 10%), and sexual dysfunction (up to 5%).
        - Rare side effects include an allergic reaction (less than 2%), changes in heart conduction causing slowing or speeding up of the heart rate (less than 1 in 100), and serotonin syndrome (symptoms include fever, sweating, fast heart rate, restless, confusion, and diarrhea; less than 1 in 100).
    - In addition, some participants may experience minor skin irritation from the adhesive used to attach the electrodes to your skin (less than 1 in 100). If you have an allergy to adhesives, please let us know.
    - There is also a possibility that your GERD-related symptoms may flare. If so, please call the research team so that a study-affiliated physician can provide recommendations.
    - Blood draws may cause a small amount of pain. In addition, you may get a temporary bruise or "black and blue mark." Rarely, people faint when their blood is drawn. Very rarely, the vein may become red and swollen or infected. If this happens, the problem can be treated.
- Psychological risks
    - Some people may feel uncomfortable being video recorded. If you do not wish to be video recorded, we will stop your participation in the study.
    - If any of the questions that we ask make you feel uncomfortable, you may refuse to answer them or take a break at any time during the study.
    - In rare instances (less than 1 in 1000), people may experience suicidal thoughts while taking amitriptyline. We are using a low dose to reduce this risk, but if you

experience such thoughts, please call the research team or go to your local emergency room.

As with all research, there is a chance that confidentiality could be compromised. To minimize the risks of breach of confidentiality, we will not include any information that directly identifies you on the information we collect, and on the data resulting from the research. Instead, we will record a code on the information, and we will keep a link between the code and your identity in a different location.

There is a risk that your information could become known to someone not involved in this study.

What about Birth Control?

Contraception Requirements for Women

The study drug may harm a fetus or a breastfeeding baby. If you are pregnant or breastfeeding, you cannot take part in this study. If you think you may be pregnant, you should not volunteer for this study. If you are able to become pregnant, you must have a pregnancy test before you begin the study. You must not get pregnant or breastfeed while you are in this study. If you are a woman who can become pregnant, you must take measures to avoid becoming pregnant while you are in this study. The following are acceptable measures to avoid becoming pregnant:

One of the following forms of birth control should be used:

- Abstinence (not having sexual relations with a person of the opposite sex)
- Implantable hormone (e.g. Norplant)
- Intrauterine Device
- Male partner must have a vasectomy
- Female sterilization
- Hormonal injection
- Oral contraceptives

You must use contraception, at least 1 month before starting study treatment unless you abstain from sexual intercourse. You must use contraception during study treatment and for at least 1 week after stopping study treatment.

Will being in this study help me in any way?

Being in this study may reduce or relieve your GERD symptoms, but we cannot promise this will happen. The study treatment might not work at all, or it might have side effects. Even if the study does not help you directly, your participation in this study may help other people in the future by helping us learn more about GERD and how people respond to amitriptyline.

What happens if I benefit from taking amitriptyline?

If you notice an improvement in your GERD-related symptoms while taking amitriptyline, a study-affiliated physician can write you a prescription for a 30-day supply of amitriptyline after the study is

over to bridge you until you have a chance to meet with your primary care physician or gastroenterologist who can evaluate you and continue prescribing the medication if it is helpful.

If you do not benefit from the amitriptyline or wish to stop the medication, a study-affiliated physician will provide you with instructions for tapering off of the medication.

Will being in this study cost me anything?

You will have to pay for basic expenses like any childcare, food, or transportation related to study activities.

If you need treatment for side effects while you are on the study, you or your insurance will need to pay for this treatment.

For more information about possible costs, please contact the research team. The research team can follow UC Davis Uninsured Non-Emergency Estimate Policy (Policy ID 1883) to work with their department and Decision Support Services to get you a cost estimate.

Will I be paid or receive anything for being in this study?

We will pay you $30 for completing Visit 1 and $50 for completing Visit 2, for a total of $80 if you complete both study visits. Payment will be provided at the end of the study in the form of check that will be mailed to you. If you choose to leave or we take you off the study for any reason, you will receive an amount proportional to the number of study visits you completed.

You will also receive a 2 month's supply of amitriptyline at no cost to you. If you decide to stop amitriptyline after the study is over, we will provide you with instructions for how to taper off this medication and additional medication, if needed, to complete the taper.

You may be asked for your social security number for payment purposes. It will not be used for any other purpose without your permission.

If you receive $600 or more during a calendar year from the University for participating in research, you may receive a 1099 for tax reporting purposes. Reimbursements for travel and other expenses are not included in this amount.

What happens if I am injured or get sick because of this study?

If you are injured or get sick because of this study, medical care is available to you through UC Davis Health, your local provider, or emergency services.
If you are injured as a result of being in this study, the University of California will provide the necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by the University or the study sponsor or may be billed to your insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, you may contact the IRB Administration at (916) 703-9151 or HS-IRBAdmin@ucdavis.edu.

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What happens to the information collected for the research?

We will do our best to limit the use or disclosure of your personal information, including information from this research study and from your medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Some organizations may be required to inspect and copy your information including the IRB and other University of California representatives responsible for the management or oversight of this study.

We have strict rules to protect your personal information and protected health information (PHI). We will limit who has access to your name, address, phone number, and other information that can identify you. We will remove identifiable information from the data we collect about you. After we remove all of the identifiers, we will place a code on the information. The code will be linked to your identity but the link will be kept in a location that is separate from your study data. We will maintain your study data on encrypted computers and access to the information will be limited to only members of the research team who need the access to properly conduct the study.

However, we cannot promise complete confidentiality. If you agree to be in this study, Federal or state laws may permit or require us to show information to university or government officials and to study sponsors responsible for monitoring this study. We may also show your medical records to study monitors, auditors, the IRB, and the FDA. These groups are obligated to maintain your confidentiality. The following is a list of individuals who may access your records:

- Members of the research team
- Offices and committees responsible for the oversight of research
- Personnel who schedule or perform medical tests or procedures, handle accounting and billing, or do other tasks related to this study
- U.S. Office for Human Research Protections
- The study sponsor, the National Institutes of Health (NIH)

If you agree to participate in this research study, a signed copy of this consent document will be filed in your electronic medical record (EMR) to ensure people caring for you at UC Davis Health will have the information they need about this research study when they provide care for you. Placing a copy of this consent form in the EMR is intended only to give information to caregivers providing treatment for you while you are on this study.

Federal and state privacy laws give patients the right to access information about their care and treatment contained in their medical record. During this study, you may not be able to access certain information related to this study in your EMR until the study is complete to ensure that the study remains unbiased. If necessary for your care, this information will be provided to you or your physician.

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

We will access protected health information (e.g., your medical record) for this study and you will be asked to sign a separate form to give your permission. Your medication list will become part of the

research record. If that happens, your medications may be looked at by the sponsor of this study and government agencies or other groups associated with the study. They may not copy or take your personal health information from your medical records unless permitted or required by law.

Federal law provides additional protections of your medical records and related health information. These are described in the UC Davis Health System Notice of Privacy Practices (http://www.ucdmc.ucdavis.edu/legal/privacy/) and in an attached document.

This research is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. The researchers with this CoC may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding. For example, the information collected in this research cannot be used as evidence in a proceeding unless you consent to this use. Information, documents, or biospecimens protected by this CoC cannot be disclosed to anyone else who is not connected with the research, except:

- To a federal agency sponsoring this research when information is needed for auditing or program evaluations;
- To meet the requirements of the U.S. FDA;
- If a federal, state or local law requires disclosure such as a requirement to report a communicable disease;
- If information about you must be disclosed to prevent serious harm to yourself or others such as child abuse, elder abuse or spousal abuse;
- If you consent to the disclosure, including for your medical treatment, to an insurer or employer to obtain information about you; or
- If it is used for other scientific research, as allowed by federal regulations protecting research subjects.

This CoC also does not prevent you or a family member from voluntarily releasing information about yourself and your involvement in this research.

Will I receive any results from this research?

No. Because we are de-identifying the data before we analyze it and not relinking the data to your identity we will not be able to share your individual results study results.

Will information or leftover specimens be used for other research?

During this research, the study team will obtain information about you. The information will be used for this research and may also be used for other research studies here at UC Davis. We may also share the information with other institutions for research. Before using the information for other research, the study team will remove information that identifies you so the individuals performing the research will not know who the information came from. We will not ask for additional consent from you to use your information for the additional research.

Are there any optional parts of the study?

This part of the consent form is about an additional, optional part of the study that you can choose to take part in. Things to know about this optional part of the study:

- This is optional. You can still take part in the main study even if you say "no" to any or all of this optional part of the study.
- This part of the study will not help you directly. We hope the results from this optional part of the study will help us to better predict in the future which patients best respond to the treatment being offered in this study.
- We will not tell you the results of this optional part of the study, and we will not put the results in your medical records.
- Taking part in the optional part of the study will not cost you anything.

The optional part of the study involves having two blood draws, one during each study visit.

We will use your blood samples to conduct genomics and metabolomics analyses to determine whether there are certain genes and small molecules in your blood that are activated in response to the study treatment and whether this information can help us to predict who will best respond to the treatment.

To maintain your confidentiality, we will freeze your processed blood samples in tubes labeled with your unique study ID so that none of your personally identifying information is on the sample. When we report the results of our analyses, we will do so only for the study as an aggregate so that no individual genetic data will be reported.

Will genetic research be done as a part of this study?

Some of the tests we will perform on your blood will be genetic testing, which is done on your DNA. DNA, or deoxyribonucleic acid, carries the genetic instructions for the cells that make up your body. Genes tell your body how to do things like form your spine, or what color your eyes should be.

The DNA samples and information sent to other researchers will not include personal information like your name or your birthdate. However, even without your name or other identifiers, your genetic information is unique to you, like a fingerprint. Scientists expect that over the next few years, researchers will be able to look at your genetic information and be able to trace the data back to you (and potentially also to your blood relatives).

There may be other risks related to genetic testing that we don't know about right now. This is because the field of genetics is moving forward very quickly.

Will My Genetic/Genomic Data Be Shared With Repositories?

At some point in the future, we will be required to share genetic data with federal repositories. Because this research receives funding from the National Institutes of Health (NIH), we will submit your genomic information to a public repository approved by NIH. NIH is a national research agency and is part of the federal government. The NIH and other central repositories have developed special data (information) banks that collect the results of genetic studies, especially when the research looks at all or large sections of individual's genetic code. This is often called whole genome sequencing. Genomic information relates to the structure and function of all of the genetic material in the body.

These central banks will store your genetic information and give them to other qualified and approved researchers to do more studies. The data that we share with federal repositories will be coded in such a way that you would not be able to be identified. We will not share your name, birth date, or any other information that could directly identify you. The link to the code would be kept securely at UCD. Even so, there is a possibility that when your genomic information is combined with other information available to researchers, either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally. NIH prohibits people from trying to identify individuals whose genomic information is in an NIH-designated repository.

We do not think that there will be further risks to your privacy and confidentiality by sharing your genetic information with these banks. However, we cannot predict how genetic information will be used in the future. The genetic data could be used to study a wide variety of diseases.

Please initial one of the lines below to indicate whether or not you agree to the optional blood draws.

____ Yes, I agree to have my blood drawn at each study visit.

____ No, I DO NOT agree to have my blood drawn at each study visit.

Will information or leftover specimens be used for other research?

We may keep your frozen samples for up to 15 years and may use them for related studies. Keeping data or samples for future research is called "banking." The banked data and samples will be kept in a secure location for use by researchers.

This is what will happen with your banked data and samples:

- We may use the data and samples in other research projects related to GERD.
- The data and samples may be shared with other researchers at UC Davis and with researchers outside of UC Davis.
- The banked data and samples will be labeled with a code instead of your name.
- When we give your data and samples to other investigators for research projects, they will not be able to use the code to figure out which data and samples are yours.
- The research team will maintain a link between your data and samples and your identifiable information kept by the study team.
- You can request to have your data and samples removed from the bank by contacting the research team at any time.

Please initial one of the lines below to indicate whether or not you agree to the optional data and samples banking:

____ Yes, I agree to have my data and samples banked for future research purposes.

____ No, I DO NOT agree to have my data and samples banked for future research purposes.

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May we contact you by e-mail?

We are requesting your email address so we can contact you to confirm study appointments and send you copies of study diaries. Email is generally not a secure way to communicate about your health, as there are many ways for unauthorized users to access email. You should avoid sending sensitive, detailed personal information by email. Email should also not be used to convey information of an urgent nature. If you need to talk to someone immediately, please contact the study research coordinator (you will be given their contact information) or Dr. Michelle Dossett, the lead study investigator*)*. You do not have to provide your email address to participate in this study. Please initial one of the lines below.

_____ Yes, may use email to contact me for this study. My email address is: _____

_____ No, I do not want to be contacted by email.

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Signature Block for Capable Adult

Your signature documents your permission to take part in this research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

Do not write below this line. For IRB stamp and version date only.

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