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EXAMINING THE ROLE OF IMPROVED NSAID MANAGEMENT IN TREATING DYSMENORRHEA AND BLADDER PAIN

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CONSENT FORM

Examining the Role of Improved NSAID Management in Treating Dysmenorrhea

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Sponsor: NorthShore University HealthSystem

EXPLANATION OF STUDY:

Introduction: You are being asked to volunteer for this clinical research study because you have painful periods.

This Consent Form gives information about the study that you can talk about with your doctor and/or family. You are being given this information to help your decision. If you have any questions, you can ask the study doctor or staff.

Why is this Study Being Done?

Naproxen, a common pain medication known as a non-steroidal anti-inflammatory drug (NSAID), is approved by the Food and Drug Administration for the treatment of pain including menstrual cramps. Not all women get relief of menstrual pain adequately from naproxen however, and this study will look at a women's individual sensory sensitivity measures to see if those might predict how well naproxen works.

This study will include a total of 30 subjects. Of those subjects, all will be from NorthShore University HealthSystem (NorthShore).

What Will Happen During the Study?

If you decide to participate in this research study, you will be asked to sign this Consent Form.

Screening Visit: You will be asked to sign this consent form before any study procedures are performed. This visit takes approximately 2- 2 ½ hours. During the screening visit, the following will be performed:

Questionnaires: The questionnaires in this study ask about any past and current pain symptoms and any medication you have taken for pain. We will also ask about your medical history, contraception history, and sexual functioning. There are also questions about your mental well-being. Some or all of these will be administered on the computer. You may choose not to answer questions that make you uncomfortable. We may also ask you to sign a records release to obtain records that are related to prior testing or treatments for any pelvic pain issues from other doctors.

Rapid Bladder Sensation Test: Participants will be asked to take the rapid bladder sensation test, which involves drinking water and rating how your bladder feels throughout the visit.

Urine sample: we will collect your urine to store for analysis (e.g., proteins, hormones).

Pelvic Floor Exam: If you have never had a gynecological exam before, a basic gynecological exam of the pelvic floor may be performed to introduce you to the internal testing procedures that will be performed at the assessment visit.

Creatinine Test: A creatinine test will be conducted to check for kidney function via blood draw.

After Screening Visit :

Daily Pain Diaries: After the screening visit, you will be asked to complete daily diaries to assess your pelvic pain, days you experience menstrual bleeding, and any use of painkillers. These will be completed online using any device connected to the internet. You will be given instructions during your screening visit.

If you previously participated in the CRAMPP study within the past 12 months: You will be provided the study medication at the screening visit. You will be asked to start the study medication on your second menstrual cycle after the screen visit

If you have NOT participated in the CRAMPP study within the past 12 months: Contact Study Staff to schedule Baseline Visit: It is extremely important that you contact study staff on the day you **start** your **first** menstrual flow after the screen visit in order to schedule your baseline visit. In some cases, staff may advise you wait more than one menstrual cycle in which case we will advise accordingly.

Baseline Visit: will be performed after one to four menstrual cycles and during your luteal Phase, which in most women takes place about 15-21days after you start your period (after ovulation and before your next menstrual period). This visit will take approximately 4-5 hours. The following will be performed:

Bladder Testing: After a bathroom break, an abdominal ultrasound will be performed by a trained clinician to measure your bladder volume. You will be asked to lie down on an exam table and have your pants removed slightly below your hip bones. A small amount of gel, safe for use on the skin, will be applied and removed after the scan is completed. The ultrasound wand against your abdomen may cause some pressure symptoms, although it should not be uncomfortable.

After drinking 20 ounces of water, you will be asked to report one by one a) first sensation of need to urinate b) first urge and c) maximum bladder capacity (defined as “when riding in a car, you would urinate on the side of the road in bumper-to-bumper traffic”). At each of these time points, the clinician will perform an ultrasound. Additionally, every fifteen minutes, you will rate your bladder urgency and bladder pain. After you reach maximum bladder capacity, you will be asked to go to the bathroom and urinate in a container. You may be asked to drink more water if you do not reach maximum tolerance after 45 or 60 minutes.

Pressure Tests

Pressure/Pain Threshold (PPT) Test: A doctor or nurse trained in this procedure will perform this test. This test uses two specially designed pressure measuring devices (algometers) to measure the amount of pressure at which you first report pain. At the point which you begin

to feel pain, we will stop applying pressure. You will be asked to rate the intensity of pain on a 0-10 scale. The algometers are investigational and have not been approved by the Food and Drug Administration (FDA). We will test the pressure at which you first report pain at several standard spots of your body using these algometers. We will measure at your right shoulder, right hip, right knee, and forehead using a handheld algometer. The tip of the handheld external algometer is made of rubber and about the same size as a pencil eraser. Then you will be helped into the stirrups and asked to lie down on the exam table. Using a small amount of lubricant, the clinician will use an internal vaginal algometer to press on the muscles near the entrance of your vagina. The vaginal algometer fits on the pad of the examiner's index finger under a glove.

Cold Water Test (also known as conditioned pain modulation (CPM) test): For this test, you will be asked to put your hand up to your wrist in a bucket of cold water (0-6° C) for about 20 seconds. The pressure measurement test will be performed on your left knee and left shoulder before you put your hand in cold water, after your hand is in the cold water for 20 seconds and five and ten minutes after you remove your hand from the cold water. After each of the pressure measurement tests, we will ask you to rate your pain on a 0-10 scale.

Repeated Pressure Measurement Test-Knee (also known as temporal summation): Using the handheld algometer, we will press on your knee up to ten times. You will be asked to rate how much pain you feel on a 0-10 scale after each press.

Sensory Testing: We will ask you to watch brief videos of colorful moving patterns and listen to sounds using headphones and tell us what you think of them.

Blood Draw: A trained doctor, nurse, or phlebotomist will collect 12 teaspoons (60 ml) of blood at the baseline visit, menses visit, and follow-up visit (total up to 36 teaspoons/180 ml) to examine factors (hormones, genes-if you give consent, proteins) that affect women's health conditions. If you give your permission at the bottom of this consent form, we may also store your blood for future research in our lab on women's health conditions beyond the current study.

Monitoring During Visit: During each assessment visit, electroencephalography (EEG), electromyography (EMG), electrocardiogram (ECG) and respiratory belt devices will be used. An EEG test allows us to measure changes in your brain's electrical activity, using an array of measuring wires placed under a cap that will fit over your scalp. An EMG test measures the electrical activity produced by your skeletal muscles, using stick-on wires applied to the skin overlying the muscle. An ECG is a test that measures the electrical activity of your heart by attaching stick-on wires to your chest and records your heart rate. The respiratory belt goes around your ribcage and monitors your rate of breathing.

After Baseline Visit (or After Screen Visit for 12 month CRAMPP participants): You will be provided study medication at the end of your visit. You will be instructed to take one 500 mg pill in the morning and one again 12 hours later the day before your anticipated first day of your period. You will continue to take a pill twice daily for the first 3 days of your menstrual period. If you still have menstrual pain the following day, you will be instructed to continue taking 2 pills a day (one in the morning and one 12 hours later) until your pain stops. You will be asked to continue taking the study medication before and during your period for 6-8 months. In the event that you have been taking the study medication for 3 consecutive days

and do not have any symptoms of starting your menses, you will be instructed to stop taking the study medication. We will instruct you to start taking it again as soon as you start your period.

You will be allowed to take acetaminophen (also known as Tylenol, according to directions listed on the package) as needed to manage any additional unrelieved pain. Do not take any other form of NSAID while you are taking the study medication.

Monthly Menstrual Diaries: Starting approximately one day before the start of your menses and up until you have stopped bleeding, you will be asked to complete daily symptom diaries. These are to assess your period pain and to log your study medication usage. They can be completed online using any device connected to the internet. Please complete the diary close to the end of the day to have the most accurate representation of that day.

Blood draw/Urine Collections: You will be asked to come in for a blood draw during your menses to measure hormones and the absorption of Naproxen. This can be done during any month after the baseline visit, but before the follow-up visit, on day 2 or later of your menses. You will be asked to collect a urine sample, in the collection containers we will provide you with, on the third day of your menstrual cycle for each period. Urine samples can be frozen and brought in at study visits or at a time agreed upon the participant and research staff.

Follow-Up Visit (month 6-8) for all participants: You will be asked to come back in for a follow-up visit after 6-8 menses. This visit takes about 4 ½ hours. You will be asked to repeat the same tasks as the baseline visit (questionnaires, bladder test, pressure tests, blood draw, and sensory test).

Does this study involve Genetic testing?

Your blood may be used for genetic testing if you give permission at the bottom of this consent form. You may still participate in this study even if you do not give permission for genetic testing of your blood. Because there are no presently established genetic markers for pelvic pain, you will not be told the results of the testing. The scientists studying the DNA genetic information at NorthShore will never receive any information that could link your name to your clinical DNA data. Likewise, scientists at NorthShore will never receive any DNA data that could be linked to your name. DNA data will be kept under lock and key, and will be accessible only to authorized personnel.

A federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

This law will generally protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information from this research.
- If health insurance companies and group health plans do somehow receive your genetic information from this research, they may not use it to make decisions about your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information from this research when making a decision to hire, promote or fire you or when setting the terms of your employment.

How Long Will I Be In the Study?

You will be in this research study for approximately 32 weeks. The figure below outlines procedures across the 6-8 months and what to expect at each visit.

		Screen Visit	Baseline Visit*	Follow-Up Visit
Schedule of Events	**Time to complete**			
Consent	30 min	X		
Questionnaires	30 min	X	X	X
Pelvic floor exam	10 min	X**		
Rapid Bladder Test		X		
Creatinine Test	10 min	X		
Bladder test	120 min		X	X
Pressure tests	45 min		X	X
EEG	60 min		X	X
Urine Samples	10 min			Urine samples on the third day of your menses
Blood draw	10 min		X	Done any time and during your menses
Participant incentive		X	X	X
Menstrual Diaries, Home checks	Variable	X		Done once a month for 6-8 months during your menstrual cycle

*Baseline Visit is only completed if you have not completed an assessment visit in EH13-094 (CRAMPP Study) in the past 12 months.
**Pelvic Floor Exam is only for those participants who have never had a gynecological exam before

***Final Visit/Early Termination Procedures*:** At the Follow-Up Visit, you will be asked to return any unused study medication.

What Other Choices Do I Have?

You do not have to take part in this study for treatment of your painful periods. You may use naproxen even if you decide to not participate in the study. Other commonly used treatments include oral contraceptives, other pain relievers, heat pads, herbal teas, etc. You may also choose no further treatment. Your doctor can explain your disease/condition and the good and bad things about each of the options. You are free to talk about your disease/condition and your health with your doctor.

Are There Benefits to Taking Part in the Study?

This study may allow doctors to learn more about why naproxen works better for some women in the treatment of painful periods and whether that may explain why some women with period pain develop other pelvic pain problems.

Taking part in this study may or may not make your health better. However, there is no proof of this. There is the possibility that your health may become worse while you are in this study.

What Side Effects or Risks Can I Expect?

The drug used in this study might have undesired effects. However, doctors do not know all the effects that may happen. Side effects may be mild or very serious. Sometimes they can be life-threatening. Some effects may go away soon after you stop taking the study drug. The effects can be serious, long lasting or may never go away. The study doctor will watch you carefully and will provide treatment for any effects. This may include taking you off the study or giving you other medications.

Side effects of naproxen: According to the FDA, short term use of naproxen, especially at low dosages, does not appear to be associated with increased risk of serious cardiovascular events. *Less than 1 in 10 using naproxen experience side effects such as upset stomach, nausea, heartburn, headache, drowsiness, or dizziness.* In the event these side effects persist, we will help you find a follow-up physician.

Questionnaires: Some of the questions you will be asked may be upsetting to you since they reflect issues that are difficult to talk about. If you become upset after answering the questions, you will have the option of talking to a trained mental health professional. If at any time you are concerned that you are in immediate danger or harm, you may also call (847) 570-2500 to talk with a crisis counselor at NorthShore.

Cessation of Painkillers: Subjects are asked to refrain from taking over-the-counter NSAIDs (such as naproxen, ibuprofen) or short-acting opioids (ex. hydrocodone or oxycodone) during their menses for the duration of the study. The most common risk associated with this is inadequate pain relief.

Pressure Tests: Pressure testing may cause temporary muscle soreness. The discomfort is expected to be limited to the testing site and self-limited in time (we will stop applying pressure after you report the first sensation of pain). Over-the-counter pain medications will be recommended after evaluation as needed. Occasionally, pain or soreness caused by the measurements may be delayed or of longer duration; it could also be severe enough to require additional pain medications.

Blood Draws: Possible side effects from blood drawing include faintness, inflammation (redness and/or warmth) of the vein, pain, bruising, bleeding at the site of puncture, or (rarely) infection.

Bladder Testing: Drinking the amount of water needed to complete the bladder testing may cause mild abdominal discomfort in certain individuals, but it is not dangerous. The discomfort is expected to be temporary, but may need to be treated in the usual way a woman does when she has worsened pain.

EEG, EMG, and ECG recording: The EEG cap and/or ECG/EMG electrodes may also be slightly uncomfortable. We can adjust the position of the EEG, EMG and ECG to make them more comfortable. Our equipment is certified to prevent any risk of electric shock.

Ultrasound: Ultrasound of the abdomen is safe. In rare cases, you may be allergic to the transmission gel and develop a mild rash of the skin. The gel will be washed off when the scan is complete, so the degree of irritation should be limited even in that situation. However, you may need to seek additional treatment for relief if a rash or skin problem were to develop.

Sensory Testing: The sounds and videos of moving patterns involve flashing lights and may be annoying or elicit a headache or nausea in sensitive individuals. Participants may stop at any time.

Reproductive Risks:

NSAIDs do not pose significant risks to a developing fetus, but in some studies have been associated with a potentially higher risk of miscarriage. A woman in this study, using NSAIDs for presumed menstrual pain, is at very low risk of actually exposing an early pregnancy to NSAIDs.

You should use effective birth control methods if you or your partner can become pregnant and you wish to be in this study. If you become pregnant during this study, you should notify the study doctor right away. If you become pregnant you may have to go off the study.

Will My Medical Information Be Kept Private?

Information from this study could be published in journals or presented at meetings. If either of these happens, your name and other personal information will not be used. The researchers running this study will try to keep your personal information private. Your study related information may be looked at by other doctors in this study]. Your research file can also be looked at by the NorthShore Institutional Review Board, other medical personnel at NorthShore who are involved in your care, or by the Food and Drug Administration (FDA).

Protected Health Information (PHI)

During this research, identifiable information about your health will be collected. In the rest of this section, we refer to this information simply as "protected health information (PHI)." In general, under federal law, PHI is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your PHI for research and why they may need to do so.

Your PHI will only be used for the purposes described in this Consent Form. Your authorization for activities described in this section does not have an expiration date.

What protected health information (PHI) will be used?

- Past, present and future medical records, including information housed in the Electronic Medical Record called "Epic," which is maintained by NorthShore University HealthSystem
- Information about research procedures, including research office visits, medical tests, procedures, interviews and questionnaires

Who may see, use and share my PHI and why may they need to do so?

- NorthShore research staff involved in this study
- Non-research staff within NorthShore who need this information to do their jobs (such as for treatment, payment (billing) or health care operations)
- The NorthShore IRB board that oversees the research and the NorthShore research quality improvement program
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other US [] government bodies that oversee or review research)

Some people or groups who get your PHI might not have to follow the same privacy rules that we follow. We share your PHI only when we must and we ask anyone who receives it from us to protect your privacy. However, if your information is shared outside NorthShore, we cannot promise that it will remain private.

Do I have the right to withdraw permission for the use of my PHI?

You have the right to withdraw your permission for us to use or share your PHI for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others.

Once permission is withdrawn, you cannot continue to take part in this study. However, you will not be penalized or lose any benefits to which you are entitled.

Do I have access to my health information?

You have the right to see and get a copy of your PHI that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. However, to protect the study, you will not be able to see some of the study information until after the study is completed. The researchers are not required to release to you research information that is not part of your medical record.

You have the right *not* to sign this form that allows us to use and share your PHI for research; however, if you do not sign it, you cannot take part in this research study.

Will I Be Paid for Participating?

You will be paid a sum of $255-$405 for being in this research study. You will be paid at the screen visit, blood draw, urine samples, and follow-up visit. You will be paid by check or, if you are an employee, paid through payroll. For payments under $20, you may be given a gift card instead depending on availability. If you do not complete the research study, you will only be paid for the length of time that you were a subject. You will be paid at the time you withdraw from the study.

Screen Visit: $25

Baseline Visit (for those who have not completed an assessment with the CRAMPP study in the past 12 months): $150

Urine samples: $60 ($10/each)

Blood draw Visit: $20

Follow-Up Visit: $150

Will There Be Additional Costs?

There is expected to be no additional cost to you from being in this research study. You will still be responsible for all costs that you would normally incur as part of routine care.

Study medication (naproxen) will be provided to you at no cost. We will also provide you with parking validation.

What If I Am Injured During the Study?

If you become hurt or sick because of being in this research study, you can get medical treatment at NorthShore. You or your health insurance plan will be billed. No money has been set aside to pay the costs of this treatment. You can ask for more information from the Research Institute of NorthShore.

Health insurance plans (including Medicare) may or may not cover costs of research-related injury or illness. You should check with your insurance company before deciding to participate in this research study. Costs not covered by insurance could be substantial.

Can I Withdraw From the Study?

Your participation in this research study is voluntary. If you decide not to be in this study, you can still get medical care as usual. If you decide to participate now, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits.

Your doctor/the sponsor may stop this study or take you out of the study without your permission. If this happens, it might be the result of a bad reaction you have. There could also be new information that your doctor learns about the safety or helpfulness of this treatment.

What Are My Rights as a Research Subject?

You may get more information about your rights from the Chairperson of the Institutional Review Board (IRB). You can also call the IRB Coordinators at 224/364-7100. These are the people you should contact about any problems or research-related injuries that happen during the research study.

By participating in this research study you do not waive any rights to which you would normally be entitled.

Will I Be Informed of New Information About the Study?

Any significant new information that may affect your participation will be given to you as soon as it becomes available.

Who Can I Call With Questions?

The study doctor and staff will answer any questions you have. If you have additional questions at any time during the study, you may contact the Principal Investigator, Frank Tu, MD, MPH**,** at telephone: 8475702521.

Permission for Genetic Testing

May we use your blood for genetic testing? You may still participate in this study even if you do not give permission for genetic testing of your blood.

☐ Yes ☐ No

Permission for Future Storage of Blood and Urine Samples

May we store your blood and urine for additional testing in our lab on women's health conditions after the study is completed? You may still participate in this study even if you do not give permission for future storage of blood and urine samples. If you do not give future permission, your blood and urine samples will be destroyed when the study is completed.

☐ Yes ☐ No

Permission to Link Your Information Between Studies

May we link your data from the present study with data from any future studies you may participate in within our lab?

☐ Yes ☐ No

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INDIVIDUAL PROVIDING EXPLANATION:

The procedures and/or investigations described in the above paragraphs have been explained to you by:

Name of Person Explaining Study (Please PRINT)	
Signature of Person Explaining Study	
Date Study Was Explained	

CONSENT TO PARTICIPATE:

I understand that the Principal Investigator and study staff will supervise the study. I have read this consent form or have had it read to me. I understand what will happen if I enroll in this research study. I understand the possible benefits and risks of the study. I have been told about all of my treatment options. I give permission for the research study procedures described in this consent form.

I have reviewed this information with the study doctor and/or staff. I have had enough time to talk about all of my questions and concerns. I willingly consent to be a part of this study. I will receive a signed and dated copy of this Consent Form.

Subject's Name (Please PRINT)	
Subject's Signature	
Date Subject Signed	