UF | Institutional Review Board
UNIVERSITY of FLORIDA

INFORMED CONSENT FORM to Participate in Research, and AUTHORIZATION to Collect, Use, and Disclose Protected Health Information (PHI)

INTRODUCTION

Name of person seeking your consent:_____

Place of employment & position: _____

Please read this form, which describes the study in some detail. Overall, we are asking you to participate in our study to understand knee osteoarthritis (OA) and/or back pain and find alternative treatment options. Currently, osteoarthritis represents a significant cause of disability worldwide, and there are few options for pain management to date. Your participation in this research study is greatly appreciated and will significantly impact our understanding of knee OA and help society as a whole.

A member of the research staff is available by phone at (352) 294-8582 to answer your questions and to confirm that you understand the study details. Your participation is entirely voluntary, and if you choose to sign this form and participate you can change your mind at any time and withdraw from the study. You will not be penalized in any way or lose any benefits, to which you would otherwise be entitled, if you choose not to participate in this study or to withdraw. If you have questions about your rights as a research participant, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

GENERAL INFORMATION ABOUT THIS STUDY

1. Name of Participant ("Study Subject")

_____

2. What is the title of this research study?

Mechanisms of Oxytocin's Analgesia in Older Adults (Short title: UCOPE Study: **U**nderstanding **C**ognition, **O**xytocin, and **P**ain in **E**lders) (UCOPE Study)

3. Who do you call if you have questions about this research study?

Co-Principal Investigators: Yenisel Cruz-Almeida, MSPH, PhD, at (352) 294-8584
Natalie Ebner, PhD, at (352) 273-2141

4. Who is paying for this research study?

The sponsors of this study are the National Institute on Aging and the McKnight Brain Foundation at the University of Florida.

5. In general, what do you need to know about this Research Study?

Agreeing to become involved in any research is always voluntary. By signing this form, you are not waiving any of your legal rights. If you decide not to participate in this research, you will not be penalized in any way and you will not lose any benefits to which you are entitled. If you have questions about your rights as a research subject, please call the University of Florida Institutional Review Board (IRB) office at (352) 273-9600.

a) In general, what is the purpose of the research, how long will you be involved?

You are being asked to participate in this research study because you have knee osteoarthritis and/or experience back pain and we are studying how a particular hormone, oxytocin, may benefit your pain experience. Oxytocin is a hormone that naturally occurs in the body and has been shown to be relevant for pain, inflammation, and thinking processes. The study is roughly 3 to 5 months, with follow up calls 3 and 6 months after study completion.

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 website at any time.

b) What is involved with your participation, and what are the procedures to be followed in the research?

Your participation will involve 8 study visits, two intervention phases, and possibly another 8 sessions in the magnetic resonance imaging scanner, if you are interested and eligible in that portion of the study. You will also be allowed to complete any of the assessments during extra visits to reduce your burden and avoid fatigue. You will undergo various testing before and after self-administering oxytocin or placebo via a nasal spray. See below (#7) for more in depth information on the procedures.

Any of the sessions may take place remotely or be condensed into one session before and after the intervention. We will do this using UF Zoom, phone calls, and/or RedCap.

c) What are the likely risks or discomforts to you?

Possible risks or discomforts to you are listed in depth on question 10. Most individuals report discomfort of the nose and throat, for example runny nose, stuffed up nose and/or congestion, and nasal irritation.

d) What are the likely benefits to you or to others from the research?

The likely benefits to you or to others from the research are listed in depth on question 11. Overall, there is potential for some direct benefit for study participation. Some participants may experience improved pain and mood. The greatest benefits and impact of this study will be for society as a whole, which wouldn't be possible without participation in research studies. Participation in this research study will help advance treatment methods for individuals with knee osteoarthritis and/or back pain.

e) What are the appropriate alternative procedures or courses of treatment, if any, that might be helpful to you?

There may be alternative procedures or courses of treatment for your osteoarthritis and only your physician can inform you the procedures you would qualify for.

Additional and more detailed information is provided within the remainder of this Informed Consent form, please read before deciding if you wish to participate in this study.

WHAT CAN YOU EXPECT IF YOU PARTICIPATE IN THIS STUDY?

6. What will be done as part of your normal clinical care (even if you did not participate in this research study)?

No clinical care is provided.

7. What will be done only because you are in this research study?

Overview: In the present study you will self-administer, via a nasal spray, a dosage of 24 International Units (IUs) of oxytocin or placebo twice a day over 4 weeks. After 4 weeks where you will receive no treatment, you will self-administer again oxytocin or placebo twice a day for 4 weeks. This study has the following parts:

- Initial screening
- 2 baseline study visits (4 baseline study visits if participating in the Magnetic Resonance Imaging portion of the study)

- 4-week intervention phase during which you will use a nasal spray twice a day and short weekly phone contact with study staff
- 2 study visits after the intervention (4 study visits after intervention if participating in the Magnetic Resonance Imaging portion of the study)
- Follow-up phone contact
- 4-week with no treatment period (or wash out) and phone contacts
- Repeat 2 baseline study visits (4 baseline study visits if participating in the Magnetic Resonance Imaging portion of the study)
- Repeat 4-week intervention phase during which you will use a nasal spray twice a day and short weekly phone contact with study staff
- Repeat 2 study visits after the intervention (4 study visits after intervention if participating in the Magnetic Resonance Imaging portion of the study)
- Repeat Follow-up phone contact one week, 3 months and 6 months
- Wear a smart watch during some days in the study

Portions of the study may be conducted remotely, via phone call, UF Zoom and/or RedCap. These portions include any questionnaires that can be emailed/mailed to you. Some portions of the study cannot be performed remotely, therefore you will be asked to attend one study visit on campus before and after the interventions to obtain necessary data prior to the intervention period. Portions of the study that cannot be performed remotely include but are not limited to: neuroimaging (MRI scan), saliva, blood and urine samples, sensory testing and questionnaires of sensitive nature that would be inappropriate to administer remotely.

All on campus study visits will be conducted at the Pain Clinical Research Unit in the Dental Tower, the Clinical Translational Research Building, and the McKnight Brain Institute at the University of Florida. The remote study visits will take place in your home, via UF Zoom, phone call, and/or RedCap. The remote visits will require Internet connection. Each visit is expected to last between 2-3 hours. The intervention phases will take place in your home. The no treatment 4-week period will take place in your home.

You will be assigned by chance, much like the flip of a coin, to receive first either oxytocin administered as a nasal spray or a placebo nasal spray or vice-versa. The placebo is a substance that looks like, and is given in the same way as, the oxytocin spray but contains no oxytocin. Neither you nor the research assistant will know which type of spray you are getting. This information is coded and securely stored away until the data is analyzed. This is called a “blind study” for that reason, but that information is available if it is needed. At some point in the study you will receive both drugs.

There is some flexibility on when the following assessments may be conducted and in general, questionnaires and other testing may be collected during any session that is most convenient for you as long as it is collected before you start taking the study treatment.

Screening and Baseline Health Assessment Visit: Together with the information obtained in the phone pre-screening that we have already conducted, the main purpose of the screening visit is to find out if you are eligible to continue in the study.

- At the beginning of this visit, we will ask you about recent activities. These may include recent exercise, drinking alcohol, eating a fatty meal, and having physical contact.
- You will undergo a Physical Examination under the supervision of the study clinician to confirm the diagnosis of knee osteoarthritis and rule out any exclusion criteria. The clinician will perform a manual examination of joint tenderness on both sides for hands, hips, and knees.
- We will ask you questions about your health condition and recent activities, we will review your current and past medical health, as well as your education and living situation. We will measure your blood pressure and pulse (called vital signs or “vitals”), your weight, waist circumference, and height, and we will review your current and past health to confirm that you are eligible and it is safe for you to participate in this study.
- A blood draw by a phlebotomist (~3 tablespoonfuls) and saliva/urine collection (~1/2 teaspoonful) will also be part of this visit. The study clinician will review the blood tests. Blood tests will also determine the level of oxytocin occurring normally in your blood and the level of inflammation in your body. Results of blood or/and urine testing may indicate that you should not participate in the study (e.g., certain test results could be out of normal range). If this is the case, we will give you a copy of your lab results, so that you may share them with your own medical provider and seek care if appropriate. If your blood draw indicates low sodium levels and your urine test indicates high osmolality level, we will repeat the blood draw. If the second blood draw indicates low sodium levels again, that would indicate you should not participate in the study. Some of the blood samples that you will be asked to provide will help us to find out how the activity of genes related to oxytocin (e.g., the oxytocin receptor gene) may impact how you perform on some tests or how you respond to the intervention. Saliva samples will be collected via a collection kit for additional DNA anaylsis. All samples will be stored in a locked space, labelled using a unique ID and without any identifiable information. If blood is not fully collected during one session, with your request, the remaining blood sample may be collected at a later session.
- You will be given additional questionnaires concerning your health, pain, sleep, activity levels, feelings and emotions, and coping styles.
- You will be given some questionnaires asking about previous experiences that may have been traumatic in nature both as a child and as an adult. You do not have to answer any questions that you do not want to answer.
- We will also ask you to complete several short tests regarding your thinking and memory. For these tests, we will ask you some questions that you will need to remember. We will also ask you to follow some commands, to write and draw some pictures and we will ask you to attend to, respond to, or remember various information presented on a computer screen.

- We will assess in detail your ability to feel sensations due to touch, vibration, and changes in temperature on your skin at several locations, some pre-selected (i.e., hands and feet) and some unique to you (in an area where you experience chronic pain). **You can stop any of these procedures at any time.** A detailed explanation is listed below.

- We may train you how to use a smart watch or a ring to record your pain, mood, and activities. You may wear this watch/ring during some portions of the study to record your daily physical activities (e.g., number of steps you take) as well as your pain and emotion ratings throughout the day. At the end, you will return the smart watch/ring to the study coordinators.
- If you are a female under the age of 62, you will undergo a urine pregnancy test.
- At the end of this session, we will take you to get a knee x-ray at UFHealth.

If after this first visit, we determine that you are not eligible for this study because you have a condition that interferes with the study or the study would put you at risk, you will still be compensated for your time.

Baseline Sensory Testing Visit: In the second baseline study visit, you will be asked to participate in the following:

- At the beginning of this visit, we will ask you about recent activities again like in the visit before. We will also take your vital signs again.
- You will also receive the nasal spray and be shown how to administer it. During the session, you will self-administer the spray which contains either oxytocin or placebo.
- We will assess in detail your ability to feel sensations due to touch, vibration, and changes in temperature on your skin at several locations, some pre-selected (i.e., hands and feet) and some unique to you (in an area where you experience chronic pain). **You can stop any of these procedures at any time.**
  - Touch Sense: We will measure your touch sensitivity by applying small, plastic, blunt-tipped sticks (filaments) of differing thickness against your skin. The larger filament is about the thickness of a toothpick and the smaller is about three-quarters that size. We will touch your skin with one filament at a time and ask you to tell us if you feel any painful sensation. If you have pain, we will also assess your pain response to touch that is normally not painful by using another plastic filament about one-third the thickness of a toothpick lightly tapping your skin 1 to 10 times. Additionally, we will brush your skin with a soft-bristle paintbrush 1 to 10 times.
  - Vibration Sense: We will use a small blunt device that vibrates more and more vigorously over time, and you will be asked to let us know when you first start to feel the vibration. We will repeat this procedure 3 times at each test site (hands, feet, and painful areas).

- Temperature Sense: A small metal heating/cooling surface, about the size of two adjacent postage stamps, will be placed on your skin. You will be asked to tell us when you first feel coolness, warmth, or pain due to cold or heat. We will repeat this test 3 or 4 times at each site. The metal heating/cooling surface is not able to reach temperatures, or be of a duration, that could cause tissue damage to your skin. The machine has built-in safety features and algorithms to ensure participant's safety.
- Sensitivity to Heat: One type of sensation will be produced by a small heat probe, or heated metal plate placed on your skin, that will increase in temperature. You will feel several different levels of heat. Some of these temperatures might cause you to experience pain. You will be asked to tell the researcher how the heat feels to you by rating the sensation using numbers or a sliding scale. For your safety, the small heat probe is not able to reach temperatures, or be of a duration, that could cause tissue damage to your skin. The machine has built-in safety features to ensure this.
- Sensitivity to Cold: A second type of sensation will be produced by a small cold contact placed on your skin that will decrease in temperature. You will feel several different levels of cold. Some of these temperatures might cause you to experience pain. You will be asked to tell the researcher how the cold feels to you by rating the sensation using numbers or a sliding scale. For your safety, the small cold contact does not reach temperatures, which would cause tissue damage to your skin.
- Pressure Sense: Another type of sensation will be produced by a device that will be pressed against the skin for several seconds. This might produce pressure pain, similar to what you would feel if you pressed your finger against your skin. You will be asked to press a button and give a rating to indicate how the pressure feels to you.
- Pinprick Pressure: We will also apply a series of weighted pinprick probes. The probes will not penetrate your skin. We will ask you to tell us which probes produce pain, and then a weighted probe will be applied several times in a row and you will be asked to rate the pain experienced from the probe. In addition, we will apply a small, plastic, pinprick device to your hand and foot and you will be asked to rate the level of pain you experience at each site.
- Combined Heat and Cold Test: We will also conduct some heat and cold pain testing procedures to assess how the heat pain feels by itself, and then we will test how the heat pain feels after you remove your hand from a cold-water bath. First, we will have you rate several heat pulses. Then, we will ask you to put your hand into the cold water for up to a minute. After you take your hand out of the cold water, we will ask you to rate the heat pulses one more time.

- Before and after the sensory testing procedures, several physical measures will be taken including:

- Blood Pressure and Heart Rate: We will measure your blood pressure and heart rate with a device that attaches to your arm.
- Temperature: We will measure the temperature of your skin. This will tell us about how stressed you are. We use round flat sensors, about the size of a dime, that are taped to the skin in places such as your arm, leg, or finger. You will not have any sensation where these sensors are attached to your skin.

- We will also assess your ability to count your own heart beats as well as hear sounds while measuring your heart rate.
- We will also perform tests of your physical ability that include:
  - Standing up from a chair
  - Balance tests
  - Muscle strength tests of your arm and leg

Baseline Neuroimaging Visits (up to 2):

- At the beginning of this visit, we will ask you about recent activities.
- We will take pictures of your brain at rest and while at work using magnetic resonance imaging (MRI). MRI is a procedure that allows study of the brain and body non-invasively using magnetic fields, and is a relatively safe and common practice. During the MRI procedure, we will ask you to rate your pain and to perform some memory/concentration tasks including your ability to count your own heartbeat.
- During the MRI, we will apply a series of heat sensations, which may or may not be painful.
- We will also ask you to respond to text and images shown on a computer screen to examine changes in your brain when you are thinking and concentrating. This activity will require you to think about, and respond to, the stimuli shown to you, then answer questions. Some of these tests are meant to be difficult, but you do not have to answer them if you do not want to.
- We will also measure chemical changes in your brain at rest using a non-invasive technology called magnetic resonance spectroscopy or MRS for short.
- We will also assess your ability to interpret your interoception. We will do this by measuring your heart rate and asking you to count your own heart beats and/or auditory tones. During this, we may also assess your ability to interpret your interoception during pain stimulation using the same heat thermode described above.

If an obvious gross abnormality is discovered during your MRI scan, the PIs will be notified immediately. Per the standard protocol of our neuroimaging facility, the on-call licensed radiologist will receive the scans for review. The radiologist will contact you and encourage you to seek further evaluation and follow-up.

Study Medication Period 1: In the 4-week intervention phase, you will be asked to engage in the following:

- You will self-administer either oxytocin or a placebo into your nose by using a nasal spray. The spray will be administered twice a day, at around 8-9AM and again at around 5-6PM, over 4 weeks. We will give you guidance about how to administer the spray and will ask you to keep a logbook of your oxytocin/placebo administration (specifically, you will log whether you took the nasal spray or not).
- In addition, on some days, we will ask you to fill in a short diary about activities you engaged in during your day, as well as thoughts and emotions you experienced and experienced stress and sleep patterns.
- You may also wear the smart watch device that was shown to you in the previous visit. . Every day you will record your pain and emotion ratings as well as if you took any pain medications. The device will also automatically record your physical activity levels.
- We will call you once a week during the intervention phase, to ensure proper remote download of data from your smart watch to a secure research server. We will also call you to ask you whether you experience any nasal spray side effects or any problems with your health.
- We will provide the nasal spray and the smart watch for the duration of the intervention phase. When the study is complete, you will return both to the study coordinator.

Post-Intervention Health Assessment Visit: In the first post-intervention study visit you will be asked to participate in the following:

- At the beginning of your visit, we will ask you questions about your health condition, any side effects from the intervention period and recent activities.
- You will again be physically examined (including vitals) under the supervision of the study clinician.
- Another blood draw (~3 tablespoonful) will be conducted by the phlebotomist to run blood tests and determine the level of oxytocin after the intervention phase, as well as the level of inflammation in your body and some genetic and epigenetic markers, as mentioned above. Urine (~1/2 teaspoonful) will be collected again. The samples will be stored in a locked research space, labeled using a unique ID and without any identifiable information
- We will again ask you to participate in a series of tests measuring your pain, cognitive, and physical functioning. These measures will be very similar to the ones you did before the intervention phase.

Post-Intervention Sensory Testing Visit: This visit will be exactly like the Sensory Testing described before the Intervention Phase.

Post-Intervention Neuroimaging Visits (up to 2): We will ensure that you are eligible and safe to participate in the MRI/MRS scanning session on days of testing. These visits will be exactly like the Neuroimaging before the intervention.

No Intervention Period: During 4 weeks after the first study treatment, you will not receive any medication. You will receive a follow-up call at the end of the first week during this period. This call is to inquire whether you experienced any nasal spray side effects or health problems from the first part of the study.

Screening and Baseline Health Assessment Visit: This visit will be exactly like the Screening and Baseline Health Assessment Visit.

Baseline Sensory Visit: This visit will be exactly like the Baseline Sensory Testing Assessment Visit.

Baseline Neuroimaging Visits (up to 2): These visits will be exactly like the Baseline Neuroimaging Assessment Visit. We will ensure that you are eligible and safe to participate in the MRI/MRS scanning session that day.

Study Medication Period 2: This period will be exactly like the Study Medication Period 1. The only difference is you will self-administer the drug you did not receive during the first study period.

Post-Intervention Health Assessment Visit: This visit will be exactly like the Health Assessment described before the Intervention Period.

Post-Intervention Sensory Visit: This visit will be exactly like the Sensory Testing before the intervention.

Post-Intervention Neuroimaging Visits (up to 2): These visits will be exactly like the Neuroimaging described before the Intervention Period. We will ensure that you are eligible and safe to participate in the MRI/MRS scanning session that day.

Upon completion of the study, we will tell you about the general goals of the study and answer any questions that you may have.

Follow-Up Phone Call: We will call you about one week, 3 months and 6 months after your last study visit to inquire whether you experienced any nasal spray side effects or any health problems. This phone call will consist of questionnaires already exposed to the participant.

If you participate in this research study, as mentioned above, we will collect blood and urine samples in separate containers for laboratory tests. The samples will be stored in a locked research space at the University of Florida. We will use the samples to measure oxytocin levels in your blood, genetic markers related to oxytocin, and various inflammatory marker levels.

When there is no longer sufficient amounts of blood and urine samples collected from you for analysis, or samples become degraded, or you request in writing that we destroy it, any remaining genetic material will be destroyed. The samples will only be accessible to the research staff and will be labeled only by an identification number, not your name. The University of Florida will not sell the samples and will not use the DNA for cloning.

You can stop any procedure or test at any time by simply telling us to stop. Furthermore, if you have any questions now or at any time during the study, or if you have any discomfort or concerns during or after the study, you are encouraged to get in contact with the Principal Investigators listed in question 3 of this form.

Once this research study is completed, any information that could identify you might be removed from any identifiable private information or identifiable biospecimens collected. After such removal, the information or biospecimens could be used for future research studies, or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

If you have any questions now or at any time during the study, please contact one of the research team members listed in question 3 of this form.

8. How long will you be in this research study?

The entire study is expected to expand over a time period of approximately 3-5 months, comprising the following components with time estimates:

Study Period 1:

- Baseline Health Assessment Visit: 2-3 hours
- (up to 2) Baseline Neuroimaging Visits: 2-3 hours
- Baseline Sensory Testing Visit: 2-3 hours
- Intervention Period: 4 weeks. Study-related activities during this phase are expected to take 15-20 minutes each day including watch participation and a short phone call once a week (about 20 minutes)
- Post-Intervention Health Assessment Visit: 2-3 hours
- (up to 2) Post-Intervention Neuroimaging Visits: 2-3 hours
- Post-Intervention Sensory Testing Visit: 2-3 hours
- Follow-Up Phone Call: 5 minutes

No Treatment (Wash-out) period:

- 4 weeks. Study-related activities during this phase are expected to take 15-20 minutes each day including a short phone call once a week (about 20 minutes).

Study Period 2:

- Baseline Health Assessment Visit: 2-3 hours
- (up to 2) Baseline Neuroimaging Visits: 2-3 hours
- Baseline Sensory Visit: 2-3 hours
- Intervention Period: 4 weeks. Study-related activities during this phase are expected to take 15-20 minutes each day including watch participation and a short phone call once a week (about 20 minutes)
- Post-Intervention Health Assessment Visit: 2-3 hours
- (up to 2) Post-Intervention Neuroimaging Visits: 2-3 hours
- Post-Intervention Sensory Visit: 2-3 hours
- Follow-Up Phone Calls: 15 minutes each

Altogether, the study requires no more than 8 to 16 visits, spanning 25 to 40 hours respectively.

9. How many people are expected to take part in this research study?

We plan to screen up to 2000 participants and expect 160 people to complete the study.

WHAT ARE THE RISKS AND BENEFITS OF THIS STUDY AND WHAT ARE YOUR OPTIONS?

10. What are the possible discomforts and risks from taking part in this research study?

Equipment used in this research meets all current safety standards and research staff is highly trained in the use of all equipment. There are no known physical or economic risks to participants and minimal, if any, known psychological risk from any of the procedures. This study may include risks that are unknown at this time. The reported side effects include increased calmness/euphoria, lightheadedness, drowsiness, headache, nasal irritation, and dry mouth/throat. Throughout the study, the researchers will notify you of new information that may become available and might affect your decision to remain in the study.

Oxytocin Nasal Spray Application: There is previous scientific evidence, including data from our own lab, demonstrating that, when oxytocin is delivered in similar doses (18-40 IU) over extended periods of several weeks in a controlled research study, as in the present study, the use of oxytocin nasal spray produces no consistent side effects and provides no known risk to participants who meet the study's eligibility criteria. The following adverse effects have been reported: headaches, faster or slower heart rates, vomiting and discomfort of the nose.

However, the oxytocin spray is a new type of investigational drug and there is the possibility that there are risks of its use that we do not know about at this time. During the intervention phase and one week after study completion, you will respond to questions to detect any possible side effects or discomfort related to drug administration. Throughout the study, the researchers will notify you of new information that may become available and might affect your decision to remain in the study.

Magnetic Resonance Imaging (MRI)/Magnetic Resonance Spectroscopy (MRS): MRI and MRS are non-invasive procedures that allow study of the brain and body non-invasively using magnetic fields and radio waves. These procedures are used routinely for medical care and are very safe for most people, but you will be monitored during the MRI/MRS scans in case any problems occur.

The risks of MRI/MRS are:

- The MRI/MRS scanner contains a very strong magnet. Therefore, you may not be able to have the MRI/MRS if you have any type of metal implanted in your body, for example, any pacing device (such as a heart pacer), any metal in your eyes, or certain types of heart valves or brain aneurysm clips. The research staff will ask you questions about this every time before you have the MRI/MRS.
- There is not much room inside the scanner. You may be uncomfortable if you do not like to be in close spaces ("claustrophobia"). During the procedure, you will be able to talk with the research staff through a speaker system, and, in the event of an emergency, you can tell them to stop the scan.
- The scanner produces a loud hammering noise, which has produced hearing loss in a very small number of people. You will be given foam earplugs that will be placed inside your ear canal and headphones that cover your ears entirely, to reduce this risk.
- If an obvious gross abnormality is discovered during your MRI scan, the PIs will be notified immediately. Per the standard protocol of our neuroimaging facility, the on-call licensed radiologist will receive the scans for review. The radiologist will share his/her findings with the PIs, and one of the PIs will contact you within a day of receiving the findings and encourage you to seek further evaluation and follow-up.
- You will be monitored very carefully while in the scanner, and repeatedly checked upon to ensure comfort. At the end of the MRI/MRS scan, you will respond to a questionnaire to detect any possible discomfort related to the MRI/MRS scanning.

Knee X-Ray: This research study involves exposure to radiation from a knee x-ray. The radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation that you will receive in this study is less than 1 mrem, and is equivalent to one additional day of natural background radiation to which people in the United States receive each year. The risk from this radiation exposure is considered to be minor when compared with other everyday risks. However, the effects of radiation add up over your lifetime. Repeated exposures may increase your risk of injury or disease. When deciding to enter this study you should consider previous and future potential exposures. Examples would include x-rays taken for a broken bone or radiation therapy treatments for cancer. The investigator will provide you with a contact person if you would like more information about radiation exposure.

Blood Draw: The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure.

Genetic Testing: A Federal law, called the Genetic Information Nondiscrimination Act (GINA), makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. Additional information can be obtained at: http://irb.ufl.edu/gina.html or call 1-800-669-3362. If you think this law has been violated, it will be up to you to pursue any compensation from the offending insurance company and/or employer. Questions

17-21 in this form discuss what information about you will be collected, used, protected, and shared.

Blood Pressure Measurement: Placing a blood pressure cuff on your arm may cause pinching or slight bruising.

Physical Tests: There is a risk of losing your balance and falling, development of chest discomfort due to spasm of heart vessels, or being short of breath, due to heart failure or lung disease, that could be associated with the physical ability testing (e.g., the ¼ mile walk test, balance tests, rising from a chair). We will minimize this risk by: (i) safely escorting you to chairs located along the walking course should you become unsteady; (ii) following you at a close distance; and, (iii) being at your side should you need assistance. Additionally, you may experience very minor muscle soreness following some of the physical testing. This soreness usually disappears completely after 2 days. To minimize risk, only trained study team members will oversee the physical performance tests.

Cognitive Tests: There is a risk that you will find the memory and concentration tests stressful, and you might feel tired or sad because it may be difficult to remember things that you are asked to remember. You may skip any question you do not wish to answer. Research staff will explain what to do and help you take the tests during your study visits.

Sensory Testing: The sensory testing procedures may be uncomfortable or unpleasant, in that you may experience some temporary discomfort from the thermal, pressure, and mechanical stimulation. However, if you feel the sensation is greater than you wish to tolerate, you can stop any of the procedures at any time.

Thermal Injury: The risk of burn injury as a result of overheating contact thermode due to technical malfunction is very unlikely because the subject: (1) is free to withdraw from the thermode; (2) has the option to stop the stimulus at any point. In addition, the stimulator incorporates automatic safety features that do not depend on actions of the investigator or subject; (3) a safe range (max 52 degrees C) is programmed into the system preventing accidental use of potentially harmful temperature set-points; (4) the software continuously monitors thermode temperature and automatically interrupts thermode contact with the skin when the process value exceeds the set-point by > 1 degree C.

The Smartwatch: Wearing the Smartwatch has the same physical risks of wearing a normal wrist watch. While unlikely, you might notice some skin irritation or redness where you wear the Smartwatch, if you are not used to wearing a watch. Additionally, the Smartwatch cannot make any phone calls on its own, so if there is a medical emergency at any time, please call 911 yourself. Finally, there is a minor risk that the watch could be stolen and the location information of the watch could be used by the thief. To augment security, information sent by the Smartwatch is stored on a secure computer and is password protected. Only authorized personnel have access to research information, and no names, social security numbers, or personal information will be stored on the Smartwatch.

The OURA ring: Wearing the OURA ring has the same physical risks of wearing a normal ring. You can wear your Oura Ring 24/7; It's built for all day comfort. It is waterproof up to 100m/328 ft. While unlikely, if you experience skin irritation/redness on your finger, remove the product immediately. In case the ring gets stuck on your finger: Use cold water and a small amount of soap, wet your finger, and slowly twist the ring to remove it. Hold your hand up above your heart until the blood pressure gets lower, and then try the removal. In case of emergency, cut the ring with a ring cutter from the ring's thinnest point, but do not cut on the flat part of the ring. This prevents the battery from being cut. In the unlikely event that fluids from the battery come in contact with your skin or eyes, flush it out with water and seek immediate medical attention.

Finally, there is a minor risk that the ring could be stolen, if this happened, there is no way to get information from the ring because it is associated with the OURA application we installed in your phone. Only authorized personnel have access to research information, and no names, social security numbers, or personal information will be stored on the OURA application.

Your Personal Information: Some of the questions you will be asked may be personal in nature and may make you uncomfortable. Time will be made to talk with you if you appear to be distressed. In addition, we will be asking you for information about sensitive issues, such as your mood and thoughts of suicide, which may make you feel uncomfortable. If you are uncomfortable answering these questions, you can choose not to answer and discontinue participation in the study. Some people, when asked such questions, experience strong emotional reactions that may require counseling. If you do have such reactions, you are strongly encouraged to tell the Principal Investigators, who can make an appropriate referral. If we find that you are suicidal, you will be excluded from further participation in the study, and an appropriate referral will be made. If we should discover, based on the questionnaires, that you experience marked depression or suffer from another psychiatric condition, we will offer to make an appropriate medical, psychiatric, and/or psychological referral.

All participants' data will be stored de-identified (i.e., removal of all information that identifies you) in a locked space and/or password-protected computers and kept confidential to all outside the immediate research team. Participants will only be identifiable by ID number, and any publications resulting from the study will not refer to or identify individuals.

Researchers will take appropriate steps to protect any information they collect about you. However, there is a slight risk that information about you could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass you, or possibly affect your insurability or employability.

Participation in more than one research study or project may increase any risks to you. If you are already enrolled in another research study, please inform the Principal Investigators listed in question 3 of this form before enrolling in this study.

If you decide to end your participation in the study at any time, let the researcher know and we will stop.

If you wish to discuss the information above, or any discomforts you may experience, please ask questions now and/or call the Principal Investigators listed in question 3 in this form.

11a. What are the potential benefits to you for taking part in this research study?

There will not be potential benefits to all study participants. It is possible that some participants may gain direct benefit from study participation such as improved pain and mood. However, we also expect that some individuals will not receive any direct benefits.

11b. How could others possibly benefit from this study?

Study results will increase our understanding of pain and cognition in aging and the role oxytocin nasal spray may play in treatment. Such knowledge may be implemented in intervention programs that may have the potential to increase function and personal well-being.

11c. How could the researchers benefit from this study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigators may benefit if the results of this study are presented at scientific meetings or in scientific journals.

12. What other choices do you have if you do not want to be in this study?

If you do not want to take part in this study, tell the person reviewing this consent or the Principal Investigators listed in question 3 of this form and do not sign this Informed Consent Form.

13a. Can you withdraw from this study?

You are free to withdraw your consent and to stop participating in this study at any time. If you do withdraw your consent, you will not be penalized in any way and you will not lose any benefits to which you are entitled.

If you decide to withdraw your consent to participate in this study for any reason, please contact the Principal Investigators listed in question 3 of this form.

If you have any questions regarding your rights as a research participant, please call the Institutional Review Board (IRB) office at (352) 273-9600.

13b. If you withdraw, can information about you still be used and/or collected?

If you withdraw from the study, we will use only the information that was collected before your withdrawal. No additional data will be collected from you. You can ask, in writing, for the blood and urine samples to be destroyed at any time if you change your mind about contributing to the study. For this purpose, a list linking your name with your study code will be stored in a locked space and/or password protected computers and kept confidential to all outside the immediate research team. However, information may still be used and shared with others if the researchers have relied on it to complete the research.

13c. Can the Principal Investigators withdraw you from this study?

You may be withdrawn from the study without your consent for the following reasons:

- You do not follow the instructions given to you by the study team
- It is not safe for you to continue your study participation
- Unforeseen administrative reasons

Ask the Principal Investigators listed in question 3 of this form if you would like more information about this.

WHAT ARE THE FINANCIAL ISSUES IF YOU PARTICIPATE?

14. If you choose to take part in this research study, will it cost you anything?

Study Drugs

Synthetic Oxytocin, will be provided at no cost to you while you are participating in this study.

Study Services

The Sponsor will pay for or provide all study services/activities required as part of your participation in this study. There will be no cost to you. If you receive a bill related to this study, please contact Yenisel Cruz-Almeida, MSPH, PhD, at (352) 294-8584 or Natalie Ebner, PhD, at (352) 273-2141.

Items/Services Not Paid for by the Sponsor

Any other medical services provided to you that are not directly required by this study will be billed to you or your insurance company in the usual manner.

15. Will you be paid for taking part in this study?

Yes. You will receive be compensated in the form of a pre-paid, reloadable VISA card issued by the University of Florida or by cash payments. Payments are broken

down by visits ($75 per visit), the four week interventions ($75 for each intervention) and additional compensation for returning all study materials ($75). The MRI portion of the study is optional, which would decrease the number of visits needed to attend for the entire study.

For further clarification:

- If you participate in the optional MRI portion of the study, you will be asked to attend up to 18 visits ($75 per visit) plus the two interventions ($75 per intervention) and returning all materials for $75 totally up to $1,575.
- If you participate in the non-MRI portion of the study, you will be asked to attend up to 10 visits ($75 per visit) plus the two interventions ($75 per intervention) and returning all materials for $75 totally up to $975.

If you are paid more than $199 for taking part in this study, your name and social security number will be reported to the appropriate University employees for purposes of making and recording the payment as required by law. You are responsible for paying income taxes on any payments provided by the study. Payments to ***nonresident aliens*** must be processed through the University of Florida Payroll and Tax Services department. If the payments total $600 or more in a calendar year, the University must report the amount you received to the Internal Revenue Service (IRS). The IRS is not provided with the study name or its purpose. If you have questions about the collection and use of your Social Security Number, please visit: http://privacy.ufl.edu/SSNPrivacy.html.

Your payment for participation in this research study is handled through the University of Florida's Research Participant Payments (RPP)Program. Your information which will include your name, address, date of birth, and SSN (depending on amount of money you are paid) is protected. Access to the (RPP) Program site is limited to certain staff with the assigned security role. You will be randomly assigned a specific identification (ID) number to protect your identity.

If you have any problems regarding your payment contact the study coordinator.

16. What if you are injured because of the study?

If you are injured as a direct result of your participation in this study, only the professional services that you receive from any University of Florida Health Science Center healthcare provider will be provided without charge. These healthcare providers include physicians, physician assistants, nurse practitioners, dentists, or psychologists. Any other expenses, including Shands hospital expenses, will be billed to you or your insurance provider.

You will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies or

research-related injuries. Please contact your insurance company for additional information.

The Principal Investigators will determine whether your injury is related to your participation in this study.

No additional compensation is offered. The Principal Investigators and others involved in this study may be University of Florida employees. As employees of the University, they are protected under state law, which limits financial recovery for negligence.

Please contact the principal investigators Dr. Cruz-Almeida (352-294-8584or after hours 305-978-9188); or Dr. Ebner (352-273-2141 or after hours 203-691-0371) if you experience an injury or have questions about any discomforts that you experience while participating in this study.

17. How will your health information be collected, used and shared?

If you agree to participate in this study, the Principal Investigators will create, collect, and use private information about you and your health. This information is called protected health information or PHI. In order to do this, the Principal Investigators need your authorization. The following section describes what PHI will be collected, used and shared, how it will be collected, used, and shared, who will collect, use or share it, who will have access to it, how it will be secured, and what your rights are to revoke this authorization.

Your PHI may be collected, used, and shared with others to determine if you can participate in the study, and then as part of your participation in the study. This information can be gathered from you or your past, current or future health records, from procedures such as physical examinations, x-rays, blood or urine tests, or from other procedures or tests. This information will be created by receiving study treatments or participating in study procedures, or from your study visits and phone calls. More specifically, the following information may be collected, used, and shared with others:

- Contact information for purposes of scheduling;
- Information provided in questionnaires, medical exams, and tasks for purposes of the research study only; Laboratory tests used to determine eligibility; Blood specimens to be used in testing for genetic differences in oxytocin activity
- Contact information and social security number for compensation purposes only.
- However, the information/samples collected above will only be used to answer the specific questions in the present study, and not for other future studies.

This information will be stored in locked filing cabinets or on computer servers with secure passwords, or encrypted electronic storage devices until the completion of

the study. All data entered into computers or electronic storage files are assigned subject ID numbers that are de-identified to ensure that all information is protected.

Some of the information collected could be included in a "limited data set" to be used for other research purposes. If so, the limited data set will only include information that does not directly identify you. For example, the limited data set cannot include your name, address, telephone number, SSN, photographs, or other codes that link you to the information in the limited data set. If limited data sets are created and used, agreements between the parties creating and receiving the limited data set are required in order to protect your identity, confidentiality and privacy.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You have been informed that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. That is, if you give written consent for the release of information to any person, we cannot withhold that information and we cannot hold responsibility for how that person may use your information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances: If we learn about child abuse, elder abuse, or intent to harm yourself or others, we will report that to appropriate authorities.

18. For what study-related purposes will your protected health information be collected, used, and shared with others?

Your PHI may be collected, used, and shared with others to make sure you can participate in the research, and to evaluate the results of the research study. More specifically, your PHI may be collected, used, and shared with others for the following study-related purpose(s):

- To determine if you are eligible to participate in this study (including to determine if you have knee osteoarthritis and/or experience back pain);

- To determine factors influencing how oxytocin may benefit your pain experience.

Once this information is collected, it becomes part of the research record for this study.

19. Who will be allowed to collect, use, and share your protected health information?

Only certain people have the legal right to collect, use, and share your research records, and they will protect the confidentiality of these records. These people include:

- The Principal Investigators as listed in question 3 of this form and research staff associated with this project
- Other professionals at the University of Florida or Shands hospital that provide study-related treatment or procedures
- The University of Florida Institutional Review Board (IRB; an IRB is a group of people who are responsible for looking after the rights and welfare of people taking part in research)

20. Once collected or used, who may your protected health information be shared with?

Your PHI may be shared with:

- The study sponsor (listed in question 4 of this form)
- United States agencies that are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections

Otherwise, your research records will not be released without your permission except under the conditions noted above. It is possible that once this information is shared with authorized persons, it could be shared by the persons or agencies who receive it and it would no longer be protected.

21. If you agree to take part in this research study, how long will your protected health information be used and shared with others?

Your PHI will be collected, stored in a secure database, used, and shared until the end of the study. If you withdraw, in writing, your permission for the use and sharing of your PHI, your information will be removed from the database.

You are not required to sign this consent and authorization or allow researchers to collect, use, and share your PHI. Your refusal to sign will not affect your treatment, payment, enrollment, or eligibility for any benefits outside this research study. However, you cannot participate in this research unless you allow the collection, use and sharing of your protected health information by signing this consent and authorization.

You have the right to review and copy your PHI. However, we can make this available only after the study is finished.

You can revoke your authorization at any time before, during, or after your participation in this study. If you revoke it, no new information will be collected about you. However, information that was already collected may still be used and shared with others if the researchers have relied on it to complete the research. You can revoke your authorization by giving a written request with your signature on it to the Principal Investigators.

You can request removal of your data, but this must be done in writing to: Dr. Yenisel Cruz-Almeida, Ph.D., Department of Community Dentistry & Behavioral Science, P.O. Box 103628, Gainesville, FL 32610 or Dr. Natalie Ebner, Ph.D., Department of Psychology, University of Florida, P.O. Box 112250, Gainesville, FL 32611.

SIGNATURES

As an investigator or the investigators' representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; the alternative to being in the study; and how the participant's PHI will be collected, used, and shared with others.

Signature of Person Obtaining Consent and Authorization	Date

You have been informed about this study's purpose, procedures, possible benefits and risks; the alternatives to being in the study; and how your PHI will be collected, used, and shared with others. You have received a copy of this form for your records. You have been given the opportunity to ask questions before you sign, and you have been told that you can withdraw your consent at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use, and sharing of your PHI as described in sections 17-21 above. By signing this form, you are not waiving any of your legal rights.

Signature of Person Consenting and Authorizing	Date