

The Human Subjects Division (HSD) strives to ensure that people with disabilities have access to all services and content. **If you experience any accessibility-related issues with this form or any aspect of the application process, email [hsdinfo@uw.edu](mailto:hsdinfo@uw.edu) for assistance.**

## INSTRUCTIONS

- **This form is only for studies that will be reviewed by the UW IRB.** Before completing this form, check [HSD's website](#) to confirm that this should not be reviewed by an external (non-UW) IRB.
- **If you are requesting a determination** about whether the planned activity is human subjects research or qualifies for exempt status, you may skip all questions except those marked with a ☐. For example **1.1** must be answered.
- **Answer all questions.** If a question is not applicable to the research or if you believe you have already answered a question elsewhere in the application, state "NA" (and if applicable, refer to the question where you provided the information). If you do not answer a question, the IRB does not know whether the question was overlooked or whether it is not applicable. This may result in unnecessary "back and forth" for clarification. Use non-technical language as much as possible.
- To check a box, place an "X" in the box. To fill in a text box, make sure your cursor is within the gray text box bar before typing or pasting text.
- For collaborative or multi-site research, describe only the UW activities unless you are requesting that the UW IRB provide the review and oversight for non-UW collaborators or co-investigators as well.
- You may reference other documents (such as a grant application) if they provide the requested information in non-technical language. Be sure to provide the document name, page(s), and specific sections, and upload it to **Zipline**. Also, describe any changes that may have occurred since the document was written (for example, changes that you've made during or after the grant review process). In some cases, you may need to provide additional details in the answer space as well as referencing a document.

## INDEX

<a href="#">1 Overview</a>	<a href="#">6 Children (Minors) and Parental Permission</a>	<a href="#">10 Risk / Benefit Assessment</a>
<a href="#">2 Participants</a>	<a href="#">7 Assent of Children (Minors)</a>	<a href="#">11 Economic Burden to Participants</a>
<a href="#">3 Non-UW Research Setting</a>	<a href="#">8 Consent of Adults</a>	<a href="#">12 Resources</a>
<a href="#">4 Recruiting and Screening Participants</a>	<a href="#">9 Privacy and Confidentiality</a>	<a href="#">13 Other Approvals, Permissions, and Regulatory Issues</a>
<a href="#">5 Procedures</a>		

## 1 OVERVIEW

**Study Title:** Social Safety Learning in the Brain Oxytocin System

**1.1 Home institution.** Identify the institution through which the lead researcher listed on the IRB application will conduct the research. Provide any helpful explanatory information.

*In general, the home institution is the institution (1) that provides the researcher's paycheck and that considers him/her to be a paid employee, or (2) at which the researcher is a matriculated student. Scholars, faculty, fellows, and students who are visiting the UW and who are the lead researcher: identify your home institution and describe the purpose and duration of your UW visit, as well as the UW department/center with which you are affiliated while at the UW.*

*Note that many UW clinical faculty members are paid employees of non-UW institutions.*

*The UW IRB provides IRB review and oversight for only those researchers who meet the criteria described in the [SOP Use of the UW IRB](#).*

University of Washington

**1.2 Consultation history.** Has there been any consultation with someone at HSD about this study?

*It is not necessary to obtain advance consultation. However, if advance consultation was obtained, answering this question will help ensure that the IRB is aware of and considers the advice and guidance provided in that consultation.*

☐ No

☒ Yes → If yes, briefly describe the consultation: approximate date, with whom, and method (e.g., by email, phone call, in-person meeting).

Email consultation with Jennifer McBride on 6/24/21 about whether to include both men and women in the study and on 7/9/21 about adding study staff to the protocol/Zipline

Email consultation with Jordyn Wheeler on 1/10/23-1/12/23 about how to submit updates to study protocol to obtain full IRB approval now that FDA approval has been secured.

Email consultation with Jordyn Wheeler on 7/11-7/13 about whether these changes needed a modification.

**1.3 Similar and/or related studies.** Are there any related IRB applications that provide context for the proposed activities?

*Examples of studies for which there is likely to be a related IRB application: Using samples or data collected by another study; recruiting subjects from a registry established by a colleague's research activity; conducting Phase 2 of a multi-part project, or conducting a continuation of another study; serving as the data coordinating center for a multi-site study that includes a UW site.*

*Providing this information (if relevant) may significantly improve the efficiency and consistency of the IRB's review.*

☒ No

☐ Yes → If yes, briefly describe the other studies or applications and how they relate to the proposed activities. If the other applications were reviewed by the UW IRB, please also provide: the UW IRB number, the study title, and the lead researcher's name.

**1.4 Externally-imposed urgency or time deadlines.** Are there any externally-imposed deadlines or urgency that affect the proposed activity?

*HSD recognizes that everyone would like their IRB applications to be reviewed as quickly as possible. To ensure fairness, it is HSD policy to review applications in the order in which they are received. However, HSD will assign a higher priority to research with externally-imposed urgency that is beyond the control of the researcher. Researchers are encouraged to communicate as soon as possible with their HSD staff contact person when there is an urgent situation (in other words, before submitting the IRB application). Examples: a researcher plans to test an experimental vaccine that has just been developed for a newly emerging epidemic; a researcher has an unexpected opportunity to collect data from students when the end of the school year is only four weeks away.*

*HSD may ask for documentation of the externally-imposed urgency. A higher priority should not be requested to compensate for a researcher's failure to prepare an IRB application in a timely manner. Note that IRB review requires a certain minimum amount of time; without sufficient time, the IRB may not be able to review and approve an application by a deadline.*

<input checked="checked" type="checkbox"/>
<input type="checkbox"/>

No

Yes → If yes, briefly describe the urgency or deadline as well as the reason for it.

**1.5 Objectives** Using lay language, describe the purpose, specific aims, or objectives that will be met by this specific project. If hypotheses are being tested, describe them. You will be asked to describe the specific procedures in a later section.

If this application involves the use of a HUD “humanitarian” device: describe whether the use is for “on-label” clinical patient care, “off-label” clinical patient care, and/or research (collecting safety and/or effectiveness data).

The purpose of the current study is to examine the potential role of oxytocin in enhancing social safety learning in social anxiety disorder. Despite the role of socially-acquired fear in theories of anxiety, no studies have examined whether social safety learning (learning safety through the safety experience of another individual) can be leveraged in treatment for social anxiety disorder, which is one of the most prevalent anxiety disorders in the U.S. and globally. Given the role of the social neuropeptide, oxytocin, in regulating social fear and safety learning, as well as avoidance and approach behavior, we propose that social safety learning is mediated by the brain oxytocin system and that oxytocin may have therapeutic promise for enhancing social safety learning (also known as vicarious extinction learning) in social anxiety disorder. In this study, we will test three specific aims: (1) To examine the effects of vicarious extinction learning in social anxiety disorder, (2) to examine whether oxytocin enhances vicarious extinction learning in patients with social anxiety disorder (SAD) as compared to healthy controls (HC), and (3) to examine sex differences in vicarious extinction learning, and whether there are sex differences in oxytocin's effects on vicarious extinction learning, between men and women (in clinical and healthy groups). We hypothesize that for Aim 1, across both groups receiving placebo, vicarious extinction will enhance safety learning, as evidenced by reduced return of fear in the reinstatement phase. For Aim 2, we hypothesize that (a) oxytocin, relative to placebo, will potentiate vicarious extinction learning based on skin conductance responses in SAD and HC, and (b) effects of oxytocin on vicarious extinction in SAD will be associated with enhanced vmPFC activity and enhanced connectivity in vmPFC-AMG-HP circuitry during reinstatement. Our hypothesis for Aim 3 is that sex will moderate oxytocin's effects on vicarious extinction learning. More specifically, (a) we expect to find sex differences in vicarious extinction learning in the placebo condition, with reduced safety learning among women, compared to men, with SAD; (b) Oxytocin, relative to placebo, will potentiate vicarious extinction learning more for men than women (regardless of clinical status); (c) Effects of oxytocin on vicarious extinction in men (regardless of clinical status) will be associated with enhanced vmPFC activity and enhanced connectivity in vmPFC-AMG-HP circuitry during reinstatement. We will directly test the effect of intranasal oxytocin or matching placebo on the brain mechanisms underlying social safety learning (also known as vicarious

extinction learning) using a novel task developed by our collaborators. 65 adults with social anxiety disorder and 65 healthy control participants will perform a task that involves three phases: (i) a standard social fear acquisition procedure while in a mock scanner, followed by (ii) a vicarious extinction and (iii) fear reinstatement test procedure, while being scanned during fMRI. Participants will receive oxytocin or placebo prior to the extinction phase. We will also measure skin conductance responses as an index of learning in each phase. Results will determine whether social safety learning improves fear regulation in social anxiety disorder, and whether oxytocin enhances this effect. Results will also determine whether oxytocin improves vicarious extinction learning in SAD by modulating relevant neural circuitry, and identify targets for intervention. Our ultimate goal is to advance novel therapeutic strategies for patients with anxiety disorders by leveraging pharmacology to target social learning processes that can be translated to the clinic.

**1.6 Study design.** Provide a one-sentence description of the general study design and/or type of methodology.

*Your answer will help HSD in assigning applications to reviewers and in managing workload. Examples: a longitudinal observational study; a double-blind, placebo-controlled randomized study; ethnographic interviews; web scraping from a convenience sample of blogs; medical record review; coordinating center for a multi-site study.*

The proposed investigation will utilize a randomized, double-blind, placebo-controlled between-subject design, such that all participants will be randomized to receive a single dose of either intranasal oxytocin or matching placebo nasal spray.

**1.7 Intent.** Check all the descriptors that apply to your activity. You must place an "X" in at least one box.

*This question is essential for ensuring that your application is correctly reviewed. Please read each option carefully.*

**Descriptor**

- ☐ 1. Class project or other activity whose purpose is to provide an educational experience for the researcher (for example, to learn about the process or methods of doing research).
- ☐ 2. Part of an institution, organization, or program's own internal operational monitoring.
- ☐ 3. Improve the quality of service provided by a specific institution, organization, or program.
- ☒ 4. Designed to expand the knowledge base of a scientific discipline or other scholarly field of study, and produce results that:
  - Are expected to be applicable to a larger population beyond the site of data collection or the specific subjects studied, or
  - Are intended to be used to develop, test, or support theories, principles, and statements of relationships, or to inform policy beyond the study.
- ☐ 5. Focus directly on the specific individuals about whom the information or biospecimens are collected through oral history, journalism, biography, or historical scholarship activities, to provide an accurate and evidence-based portrayal of the individuals.
- ☐ 6. A quality improvement or program improvement activity conducted to improve the implementation (delivery or quality) of an accepted practice, or to collect data about the implementation of the practice for clinical, practical, or administrative purposes. This does not include the evaluation of the efficacy of different accepted practices, or a comparison of their efficacy.

- ☐ 7. Public health surveillance activities conducted, requested, or authorized by a public health authority for the sole purpose of identifying or investigating potential public health signals or timely awareness and priority setting during a situation that threatens public health.
- ☐ 8. Preliminary, exploratory, or research development activities (such as pilot and feasibility studies, or reliability/validation testing of a questionnaire)
- ☒ 9. Expanded access use of a drug or device not yet approved for this purpose
- ☐ 10. Use of a Humanitarian Use Device
- ☐ 11. Other. Explain:

**1.8 Background, experience, and preliminary work.** Answer this question only if the proposed activity has one or more of the following characteristics. The purpose of this question is to provide the IRB with information that is relevant to its risk/benefit analysis.

- Involves more than minimal risk (physical or non-physical)
- Is a clinical trial, or
- Involves having the subjects use a drug, biological, botanical, nutritional supplement, or medical device.

*“Minimal risk” means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*

**a. Background.** Provide the rationale and the scientific or scholarly background for the proposed activity, based on existing literature (or clinical knowledge). Describe the gaps in current knowledge that the project is intended to address.

*This should be a plain language description. Do not provide scholarly citations. Limit your answer to less than one page, or refer to an attached document with background information that is no more than three pages long.*

Social affiliation promotes survival through access to shared resources and knowledge. In particular, having the ability to discriminate what is fearful or safe through the experiences of others, without the cost of personal learning, is highly advantageous within rapidly changing environments. For psychiatric disorders characterized by severe social avoidance, such as social anxiety disorder (SAD), social learning has been disproportionately understudied despite its role in the acquisition of fear in etiological models of anxiety. SAD is one of the most prevalent and disabling psychiatric disorders in the U.S. and globally, and 50% of individuals fail to achieve sustained clinical remission from cognitive-behavioral therapy (CBT), which is a learning-based treatment. Integrating social learning principles into modern CBT for SAD may enhance its potency and durability.

Recent work from our collaborators (Drs. Golkar and Olsson) has demonstrated an advantage of social learning in the context of discriminating fear and safety, called “vicarious extinction learning”. Observing others undergoing extinction training, in which a newly conditioned fear stimulus was no longer associated with a feared outcome, led to superior regulation of learned fear compared to traditional extinction learning. This effect was not merely due to the effects of social presence and may be associated with enhanced engagement of certain brain regions in the fear extinction circuit (the ventromedial prefrontal cortex (vmPFC) and enhanced vmPFC functional connectivity with the anterior hippocampus (HP) during a later test

of sustained extinction memory known as reinstatement). In this study, we propose that the benefits of socially-acquired safety learning through vicarious extinction are mediated by the brain oxytocin system.

Oxytocin is an evolutionarily conserved social neuropeptide that mediates a diverse range of socioemotional processes owing to its distinct release mechanisms and broad receptor distribution throughout the brain, particularly within the fear learning and extinction circuit. Increasing convergence from preclinical and human studies supports a “social salience hypothesis” that oxytocin modulates attentional salience by altering neural activity within reward, perceptual, and fear circuitry- effects which are particularly pronounced in social contexts. For example, rodent studies have revealed additional gains of fear extinction in the presence of a mating partner and central infusion of oxytocin in the lateral septum facilitates social fear extinction. In humans, oxytocin enhances fear extinction when given prior to extinction training and has the strongest stress buffering effects when combined with social support, compared to oxytocin, placebo, or social support alone. Recent evidence in animals and humans also confirms that intranasal oxytocin does reach central nervous system targets in biologically relevant amounts. These findings support oxytocin as a strong candidate pharmacologic agent for augmenting extinction-based therapies such as CBT. Thus, our primary objective is to examine oxytocin as a novel augmentation strategy for vicarious extinction learning in SAD.

In addition, human oxytocin research has systematically excluded female participants (Quintana et al., 2021). This is likely due to greater resources needed to control for gonadal hormones and timing of intranasal administration in a way that does not apply to males. A recent meta-analysis confirms suspected variation in endogenous oxytocin levels during the menstrual cycle, with the lowest levels in the early follicular phase and highest levels during ovulation (Engel et al., 2019). Preliminary evidence also suggests that estrogens stimulate oxytocin production via estrogen receptor beta functioning in female mice (Patisaul et al., 2003), which implies interactions between oxytocin and gonadal hormones, although there is a lack of human studies in this area. The bias toward studying male participants in human oxytocin research is consistent with gender inequities documented across scientific disciplines (Geller et al., 2006), and demands greater research attention given that anxiety disorders are more prevalent in women and that the advancement of valid biomarkers and novel therapeutics relies on generalizable findings for the entire population of people with anxiety disorders. Furthermore, basic fear regulatory mechanisms appear to be modulated by estrogen and dependent on the timing of menstrual cycles in animal and human studies, which suggests that sex may play an important role in the acquisition and extinction of fear (Maeng & Milad, 2016). In terms of whether oxytocin enhances learning safety vicariously through others, it is possible that its efficacy depends on characteristics of the learning model (the person who is being observed), such as sex, as oxytocin is a sexually dimorphic neuropeptide, and sex differences have already been reported in extinction (Milad et al., 2006), in safety learning (Glover et al., 2013), and in oxytocin’s effects on emotional processing circuitry (Domes et al., 2007; Domes et al., 2010).

- b. Experience and preliminary work.** Briefly describe experience or preliminary work or data (if any) that you, your team, or your collaborators/co-investigators have that supports the feasibility and/or safety of this study.

*It is not necessary to summarize all discussion that has led to the development of the study protocol. The IRB is interested only in short summaries about experiences or preliminary work that suggest the study is feasible and that risks are reasonable relative to the benefits. Examples: Your team has already conducted a Phase 1 study of an experimental drug which supports the Phase 2 study being proposed in this application; your team has already done a small pilot study showing that the reading skills intervention described in this application is feasible in an after-school program with classroom aides; your team has experience with the type of surgery that is required to implant the study device; the study coordinator is experienced in working with subjects who have significant cognitive impairment.*

Having maintained two previous Investigational New Drug applications from the FDA to study the role of oxytocin in psychiatric patients with social anxiety disorder and a related psychiatric condition, body dysmorphic disorder (BDD), I have the necessary experience to examine oxytocin in this study, and have previously found intranasal oxytocin to be a safe and promising novel therapeutic agent for modulating

socioemotional mechanisms underlying disorders characterized by severe social fear and avoidance. My previous graduate and postdoctoral work showed that acute doses of intranasal oxytocin can be given safely in certain psychiatric populations. We were among the first research groups to test the effects of oxytocin in SAD and BDD and demonstrated that its effects in these populations may be highly dependent on individual differences in attachment, rejection sensitivity, and symptom severity. This work has led to four first-author publications in this research area.

Some research from other teams has shown that administering oxytocin to those with psychiatric disorders may result in worsened symptoms or social behaviors (Shamay-Tsoory & Abu-Akel, 2016). Such mixed findings on the benefits of oxytocin may be explained by the notion that oxytocin regulates attentional salience in a manner that amplifies existing attentional tendencies (which may be in the worse direction for patients with psychiatric disorders who display disrupted attention). Studies examining extinction learning and reinstatement deficits in SAD have also yielded mixed findings (Rabinak et al., 2017; Hermann et al., 2002; Lissek et al., 2008) and no studies have yet examined vicarious extinction in this population to guide our hypothesis whether oxytocin will be successful in facilitating vicarious extinction. Our approach utilizes a rich design that will enable us to first study the effect of vicarious extinction in SAD patients in the placebo condition (to assess whether patients demonstrate deficits in vicarious extinction) before examining the effect of oxytocin on vicarious extinction. We will also take several measures, described in more detail below, to monitor and manage the safety of participants in our study through regular meetings with a data safety and monitoring board, and regular communication with the FDA and IRB through annual continuing review reports. Building upon the previous work of our collaborators, we will apply a vicarious extinction learning task they developed to a new population and assess the neural correlates of oxytocin's effects to provide mechanistic insight into potential neurobiological pathways by which oxytocin exerts its anxiolytic effects.

Lastly, a major area of my research examines core social and cognitive patterns of psychopathology underlying social anxiety disorder, and developing strategies for enhancing the robustness of existing interventions for this disorder. I have authored eight papers specifically involving the psychopathology or treatment of social anxiety disorder. I have also been a licensed psychologist since 2015 and have the necessary clinical qualifications to provide clinical oversight of this investigation.

**1.9 Supplements.** Check all boxes that apply, to identify relevant Supplements that should be completed and uploaded to **Zipline**.

*This section is here instead of at the end of the form to reduce the risk of duplicating information in this IRB Protocol form that you will need to provide in these Supplements.*

Check all That Apply	Type of Research	Supplement Name
<input type="checkbox"/>	<b>Department of Defense</b> The research involves Department of Defense funding, facilities, data, or personnel.	<a href="#">SUPPLEMENT Department of Defense</a>
<input type="checkbox"/>	<b>Department of Energy</b> The research involves Department of Energy funding, facilities, data, or personnel.	<a href="#">SUPPLEMENT Department of Energy</a>
<input checked="" type="checkbox"/>	<b>Drug, biologic, botanical, supplement</b> Procedures involve the use of <u>any</u> drug, biologic, botanical or supplement, even if the item is not the focus of the proposed research	<a href="#">SUPPLEMENT Drugs</a>

☐**Emergency exception to informed consent**

Research that requires this special consent waiver for research involving more than minimal risk

[SUPPLEMENT Exception from Informed Consent for Emergency Research \(EFIC\)](#)

☐**Genomic data sharing**

Genomic data are being collected and will be deposited in an external database (such as the NIH dbGaP database) for sharing with other researchers, and the UW is being asked to provide the required certification or to ensure that the consent forms can be certified

[SUPPLEMENT Genomic Data Sharing](#)

☒**Medical device**

Procedures involve the use of any medical device, even if the device is not the focus of the proposed research, except when the device is FDA-approved and is being used through a clinical facility in the manner for which it is approved

[SUPPLEMENT Devices](#)

☐**Multi-site or collaborative study**

The UW IRB is being asked to review on behalf of one or more non-UW institutions in a multi-site or collaborative study.

[SUPPLEMENT Multi-site or Collaborative Research](#)

☐**Non-UW Individual Investigators**

The UW IRB is being asked to review on behalf of one or more non-UW individuals who are not affiliated with another organization for the purpose of the research.

[SUPPLEMENT Non-UW Individual Investigators](#)

☐**Other REDCap Installation Attestation for Electronic Consent**

The research will use a non-UW installation of REDCap for conducting and/or documenting informed consent.

[SUPPLEMENT Other REDCap Installation](#)

☐

None of the above

- 1.10 Confirm by checking the box below** that you will comply with these basic COVID infection and risk control measures, OR that you have an exception granted by the HSD Director: (a) the only in-person interactions are essential for the study; (b) study team members and participants will wear face coverings throughout all procedures; (c) all study staff and participants will be screened for COVID-19 just prior to each research visit; and (d) no participants over the age of 85 years will be enrolled if their in-person participation is not connected with a clinical visit. See this [webpage](#) for details, including what “screening” means.

Review the HSD [website](#) for current guidelines about which in-person research activities are allowable.

☒

**Confirmed**

## 2 PARTICIPANTS

- 2.1 Participants.** Describe the general characteristics of the subject populations or groups, including age range, gender, health status, and any other relevant characteristics.

Participants will be men and women between the ages of 18 and 45 to limit the effects of age-related brain structure and function in this sample. Participants will be included in either the clinical or healthy control group. The clinical group will comprise 65 unmedicated individuals with a primary diagnosis of SAD, confirmed using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The healthy control group will

comprise 65 demographically-matched individuals without any lifetime medical, neurological, or psychiatric conditions.

## 2.2 Inclusion and exclusion criteria.

**a. Inclusion criteria.** Describe the specific criteria that will be used to decide who will be included in the research from among interested or potential subjects. Define any technical terms in lay language.

Inclusion criteria for clinical sample (N=65):

- 1) Men and women aged 18-45 (to limit age-related changes in brain structure and function)
- 2) Women must be having regular menstrual cycles, and not be taking hormonal contraception
- 3) Primary diagnosis of SAD confirmed using the Mini International Neuropsychiatric Interview (MINI)
- 4) Some psychiatric comorbidities (not listed in exclusion criteria below) will be allowed to ensure generalizable sample
- 5) Fluent in English, willing to provide informed consent, and able to comply with the requirements of the study.

Inclusion criteria for healthy sample (N=65):

- 1) Age-, sex-, and education-matched individuals based on characteristics of clinical group
- 2) No current or lifetime history of psychiatric, neurological, or medical disorders, as assessed by the MINI
- 3) Fluent in English, willing to provide informed consent, and able to comply with the requirements of the study.

**b. Exclusion criteria.** Describe the specific criteria that will be used to decide who will be excluded from the research from subjects who meet the inclusion criteria listed above. Define any technical terms in lay language.

Exclusion criteria for clinical sample (N=65):

- 1) Lifetime DSM-5 diagnoses of mania or psychotic disorder (All other Axis I comorbidities will be permitted to foster the accrual of a clinically relevant sample)
- 2) Acute suicidal ideation

Exclusion criteria for healthy sample (N=65):

- 1) Lifetime DSM-5 diagnosis of any medical, neurological, or psychiatric illness

Exclusion criteria for all groups:

- 1) Pregnancy (assessed by urine HCG test) or breastfeeding
- 2) Positive urine drug screening test result for amphetamines, cocaine, opiates, PCP, or THC (cannabis)
- 3) Women who are not having regular menstrual cycles (between 25-35 days on average), or taking hormonal contraception
- 4) History of nasal pathology (e.g., atrophic rhinitis, recurrent nosebleeds, hypophysectomy, etc.)
- 5) Current use of any psychotropic or steroid medication
- 6) Currently in psychotherapy
- 7) Current smoking/tobacco use or active substance use disorder within the past 6 months
- 8) History of serious medical illnesses (e.g., cardiovascular disease) or untreated endocrine diseases (e.g., thyroid disease, diabetes)
- 9) Positive MR screen (e.g., metal in the head or metal injury to the eyes; signs of increased intracranial pressure; implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, or ventriculo-peritoneal shunt)
- 10) History of head injury, neurological disorder, or neurosurgical procedure
- 11) Acute suicidal ideation, assessed by MINI clinical interview

**2.3 Prisoners.** IRB approval is required in order to include prisoners in research, even when prisoners are not an intended target population.

Is the research likely to have subjects who become prisoners while participating in the study?

*For example, a longitudinal study of youth with drug problems is likely to have subjects who will be prisoners at some point during the study.*

<input checked="checked" type="checkbox"/>	No
<input type="checkbox"/>	Yes

→ If yes, if a subject becomes a prisoner while participating in the study, will any study procedures and/or data collection related to the subject be continued while the subject is a prisoner?

<input type="checkbox"/>	No
<input type="checkbox"/>	Yes

→ If yes, describe the procedures and/or data collection that will continue with prisoner subjects

**2.4** Will the proposed research recruit or obtain data from individuals that are known to be prisoners?

*For records reviews: if the records do not indicate prisoner status and prisoners are not a target population, select "No". See the [GUIDANCE Prisoners](#) for the definition of "prisoner", which is not necessarily tied to the type of facility in which a person is residing.*

<input checked="checked" type="checkbox"/>	No
<input type="checkbox"/>	Yes

→ If yes, answer the following questions (i – iv).

i. Describe the type of prisoners, and their location(s):

ii. One concern about prisoner research is whether the effect of participation on prisoners' general living conditions, medical care, quality of food, amenities, and/or opportunity for earnings in prison will be so great that it will make it difficult for prisoners to adequately consider the research risks. How will the chances of this be reduced?

iii. Describe what will be done to make sure that (a) recruitment and subject selection procedures will be fair to all eligible prisoners and (b) prison authorities or other prisoners will not be able to arbitrarily prevent or require particular prisoners from participating.

iv. If the research is funded by one of these federal departments and agencies (Health & Human Services; Energy; Defense; Homeland Security; CIA; Social Security Administration), and/or will involve prisoners in federal facilities or in state/local facilities outside of Washington State: check the box below to provide assurance that study team members will (a) not encourage or facilitate the use of a prisoner's participation in the research to influence parole or pardon decisions, and (b) clearly inform each prisoner in advance (for example, in a consent form) that participation in the research will have no effect on his or her parole or pardon.

☐ Confirmed

- 2.5 Protected populations.** IRB approval is required for the use of the subject populations listed here. Check the boxes for any of these populations that will be purposefully included. (In other words, being a part of the population is an inclusion criterion for the study.)

*The WORKSHEETS describe the criteria for approval but do not need to be completed and should not be submitted.*

Population	Worksheet
<input type="checkbox"/> Fetuses in utero	<a href="#">WORKSHEET Pregnant Women</a>
<input type="checkbox"/> Neonates of uncertain viability	<a href="#">WORKSHEET Neonates</a>
<input type="checkbox"/> Non-viable neonates	<a href="#">WORKSHEET Neonates</a>
<input type="checkbox"/> Pregnant women	<a href="#">WORKSHEET Pregnant Women</a>

- a. If you check any of the boxes above, use this space to provide any information that may be relevant for the IRB to consider.

- 2.6 Native Americans or non-U.S. indigenous populations.** Will Native American or non-U.S. indigenous populations be actively recruited through a tribe, tribe-focused organization, or similar community-based organization?

*Indigenous people are defined in international or national legislation as having a set of specific rights based on their historical ties to a particular territory and their cultural or historical distinctiveness from other populations that are often politically dominant.*

*Examples: a reservation school or health clinic; recruiting during a tribal community gathering*

☒ No  
☐ Yes

→ If yes, name the tribe, tribal-focused organization, or similar community-based organization. The UW IRB expects that tribal/indigenous approval will be obtained before beginning the research. This may or may not involve approval from a tribal IRB. The study team and any collaborators/investigators are also responsible for identifying any tribal laws that may affect the research.

**2.7 Third party subjects.** Will the research collect private identifiable information about *other individuals* from the study subjects? Common examples include: collecting medical history information or contact information about family members, friends, co-workers.

*"Identifiable" means any direct or indirect identifier that, alone or in combination, would allow you or another member of the research team to readily identify the person. For example, suppose that the research is about immigration history. If subjects are asked questions about their grandparents but are not asked for names or other information that would allow easy identification of the grandparents, then private identifiable information is not being collected about the grandparents and the grandparents are not subjects.*

☒

No

☐

Yes

→ If yes, these individuals are considered human subjects in the study. Describe them and what data will be collected about them.

**2.8 Number of subjects.** Is it possible to predict or describe the maximum number of subjects (or subject units) needed to complete the study, for each subject group?

*Subject units mean units within a group. For most research studies, a group will consist of individuals. However, the unit of interest in some research is not the individual. Examples:*

- Dyads such as caregiver-and-Alzheimer's patient, or parent and child
- Families
- Other units, such as student-parent-teacher

*Subject group means categories of subjects that are meaningful for the specific study. Some research has only one subject group – for example, all UW students taking Introductory Psychology. Some common ways in which subjects are grouped include:*

- By intervention – for example, an intervention group and a control group.
- By subject population or setting – for example, urban versus rural families
- By age – for example, children who are 6, 10, or 14 years old.

*The IRB reviews the number of subjects in the context of risks and benefits. Unless otherwise specified, if the IRB determines that the research involves no more than minimal risk: there are no restrictions on the total number of subjects that may be enrolled. If the research involves more than minimal risk: The number of enrolled subjects must be limited to the number described in this application. If it is necessary later to increase the number of subjects, submit a Modification. Exceeding the IRB-approved number (over-enrollment) will be considered non-compliance.*

☐

No

→ If no, provide the rationale in the box below. Also, provide any other available information about the scope/size of the research. You do not need to complete the table.

*Example: It may not be possible to predict the number of subjects who will complete an online survey advertised through Craigslist, but you can state that the survey will be posted for two weeks and the number who respond is the number who will be in the study.*

☒ Yes

→ If yes, for each subject group, use the table below to provide the estimate of the maximum desired number of individuals (or other subject unit, such as families) who will complete the research.

Group name/description	Maximum desired number of individuals (or other subject unit, such as families) who will complete the research
	<i>Provide numbers for the site(s) reviewed by the UW IRB and for the study-wide total number; example: 20/100</i>
Patients with SAD	65
Healthy Controls	65

**2.9 COVID-19 Screening.** If there will be any in-person interactions with the subjects, describe how you will screen them for COVID-19 symptoms within the 24 hours before the interaction. Also, describe the COVID-19 screening procedures for the study staff who will interact with the subjects.

*Acceptable procedures include some type of symptom check or attestation, or a SARS-CoV-2 test with quick access to results. Symptom attestation involves an individual reviewing a list of symptoms and declaring the presence or absence of those symptoms. HSD strongly encourages adapting this Washington State Department of Health Screening Tool <https://www.doh.wa.gov/Portals/1/Documents/1600/coronavirus/Employervisitorscreeningguidance.pdf> or the UW EH&S Example Symptom Self-Attestation in this document: <https://www.ehs.washington.edu/system/files/resources/guidance-symptom-monitoring-COVID-19.pdf>. If you will test for the virus, you must also describe here whether the testing lab is CLIA-certified and how the results will be reported to the subjects.*

**The following measures will be taken to protect subjects and staff from COVID-19 for in-person study visits. Specific measures to be taken for research participants (consistent with current HSD policy) include:**

- During the in-person study visit, assessing whether subjects have any COVID-like symptoms (see list below), high risk exposures within the last 10 days, or pending COVID tests. If subjects endorse yes to any of the above, they will be asked to reschedule the study appointment.
- COVID-like symptoms include any of the following:
  - Fever (100.4 F or higher) or a sense of having a fever.
  - Cough that can't be attributed to another health condition.
  - Shortness of breath can't be attributed to another health condition.
  - Sore throat that can't be attributed to another health condition.
  - Muscle aches that can't be attributed to another health condition.
  - Respiratory symptoms, such as sore throat, runny nose, nasal congestion, or sneezing that can't be attributed to another health condition.
  - Chills or persistent shaking with chills that can't be attributed to another health condition.
  - Loss of smell or taste that can't be attributed to another health condition.
- Face masks will be required of all research participants. If the participant does not arrive with their own face mask, one will be provided to them. While undergoing fMRI, face masks will NOT be required regardless of vaccination status.

**Specific measures to be taken for staff members include:**

1. All lab personnel will be required to get vaccinated for COVID-19 and to document their vaccination.
2. Study staff will be asked to stay home and stay away from the lab site if experiencing any of the above listed symptoms of COVID-19.
3. Study staff will also be asked to stay home if they have knowingly been in close proximity to someone with COVID-19.
4. If any study staff have tested positive for COVID-19, then they will be required to immediately notify the EH&S Employee Health Center, who will inform any individual who had close contact with the ill person up to 48 hours prior to the development of symptom, and will evaluate the locations where the person spent time on campus for enhanced cleaning and disinfection.
5. To prevent transmission of COVID-19, hands will be washed upon entry to the lab. Wearing a face covering will be required when outside of individual offices. All shared equipment (e.g., computers, phones, etc.) will be thoroughly sanitized after each use with sanitizing wipes, and hand-sanitizer will be available in rooms containing shared equipment. Many sanitation areas throughout the lab space will be available for lab members to practice healthy hand hygiene and to disinfect and sanitize personal, as well as shared, workspaces. On-site lab members will be asked to avoid direct contact with other lab members (e.g., handshakes, hugs, etc.).

### 3 NON-UW RESEARCH SETTING

*Complete this section only if UW investigators and people named in the **SUPPLEMENT: Non-UW Individual Investigators** will conduct research procedures outside of UW and Harborview*

**3.1 Reason for locations.** Describe the reason(s) for choosing the locations.

*This is especially important when the research will occur in locations or with populations that may be vulnerable to exploitation. One of the three ethical principles the IRB must consider is justice: ensuring that reasonable, non-exploitative, and well-considered procedures are administered fairly, with a fair distribution of costs and potential benefits.*

**3.2 Local context.** Culturally appropriate procedures and an understanding of local context are an important part of protecting subjects. Describe any site-specific cultural issues, customs, beliefs, or values that may affect the research, how it is conducted, or how consent is obtained or documented.

*Examples: It would be culturally inappropriate in some international settings for a woman to be directly contacted by a male researcher; instead, the researcher may need to ask a male family member for permission before the woman can be approached. It may be appropriate to obtain permission from community leaders prior to obtaining consent from individual members of a group. In some distinct cultural groups, signing forms may not be the norm.*

*This federal site maintains an international list of human research standards and requirements:  
<http://www.hhs.gov/ohrp/international/index.html>*

- 3.3 Location-specific laws.** Describe any local laws that may affect the research (especially the research design and consent procedures). The most common examples are laws about:
- **Specimens** – for example, some countries will not allow biospecimens to be taken out of the country.
  - **Age of consent** – laws about when an individual is considered old enough to be able to provide consent vary across states, and across countries.
  - **Legally authorized representative** – laws about who can serve as a legally authorized representative (and who has priority when more than one person is available) vary across states and countries.
  - **Use of healthcare records** – many states (including Washington State) have laws that are similar to the federal HIPAA law but that have additional requirements.

- 3.4 Location-specific administrative or ethical requirements.** Describe local administrative or ethical requirements that affect the research.

*Example: A school district may require researchers to obtain permission from the head district office as well as school principals before approaching teachers or students; a factory in China may allow researchers to interview factory workers but not allow the workers to be paid for their participation.*

- 3.5 If the PI is a student: Does the research involve traveling outside of the US?**

☐

No

☐

Yes → If yes, confirm by checking the box that (1) you will register with the [UW Office of Global Affairs](#) before traveling; (2) you will notify your advisor when the registration is complete; and (3) you will request a UW Travel Waiver if the research involves travel to the [list of countries](#) requiring a UW Travel Waiver.

☐

Confirmed

## 4 RECRUITING and SCREENING PARTICIPANTS

- 4.1 Recruiting and Screening.** Describe how subjects will be identified, recruited, and screened. Include information about: how, when, where, and in what setting. Identify who (by position or role, not name) will approach and recruit subjects, and who will screen them for eligibility.

*Note: Per UW Medicine policy, the UW Medicine eCare/MyChart system may not be used for research recruitment purposes.*

Potential research participants will be recruited using community/online sources, in social media, our lab/CALM Clinic websites, , as well as flyers that are specific to the participant group (clinical or healthy control) posted around the UW campus and the greater Seattle Area. Participants with SAD will be recruited by direct clinician referral from any of the UW clinics or non-UW-affiliated community clinics (e.g., UW Psychology Training Clinic, UW CALM Anxiety Clinic, UWMC Outpatient Psychiatry Clinic, Evidence-Based Treatment Centers of Seattle, etc.). Interested participants will make initial contact with the study research assistant, who will respond to the interested participant using the “First Interest Reply” email template, which provides prospective participants

with information about sensitive inclusion/exclusion criteria for the study. Participants who view our online or physical advertisements will see elements found in our “First Interest Reply” email and a QR code that will take them to our website. Participants who are still interested in participating in the study will be asked to respond by indicating interest in proceeding with next steps of scheduling a preliminary phone screen interview that will take approximately 20-30 minutes. Interested participants who call instead of email will receive a call back from a trained member of the study staff providing the same information by phone to help participants self-select out of the study without going through sensitive screening questions. The phone screen interview will ask potential participants more detailed questions about their mood and mental health history to assess possible history of SAD, medical history, current medications, and contraindications to MRI.

#### 4.2 Recruitment materials.

**a. What materials (if any) will be used to recruit and screen subjects?**

*Examples: talking points for phone or in-person conversations; video or audio presentations; websites; social media messages; written materials such as letters, flyers for posting, brochures, or printed advertisements; questionnaires filled out by potential subjects.*

We will use print and online advertisements, flyers, and websites to recruit participants for the study. Online advertisements will be posted in online forums such as Craigslist, Facebook/Instagram on the UW CALM Anxiety Clinic website, UW ITHS Research recruitment pages, UW Communication Studies Participant Pool, and CoNNeCT Lab website. Flyers will be posted around the UW campus (e.g., Psychology Department, dorms, student activity centers, etc.) and around the greater Seattle area (phone poles, coffee shops, etc.), or emailed to clinicians in the community to share with their patients. Interested participants will make initial contact in one of two ways: (1) by contacting the study research team via phone or email using the contact information listed in the advertisement. The ‘First Interest Reply Email’ template will be sent to participants including a list of the inclusion/exclusion criteria and the Calendly link to sign up for a phone screen. (2) by signing up directly for a phone screen slot on Calendly using the link on the advertisement. All recruitment pages and ads will use the same language as the First Interest email reply template so that all interested participants will get the same information regardless of whether they signed up directly for a phone screen or emailed/called first. Flyers will contain a condensed version of information on the “First Interest Reply” email template to make them easier to read (see “Ad Description” attachment) and will include two versions to recruit from the social anxiety clinical population and the healthy control population. We will use the attached “Phone Screen” document to conduct a phone screen interview, which will help determine preliminary eligibility for interested participants.

**b. Upload descriptions of each type of material (or the materials themselves) to *Zipline*. If letters or emails will be sent to any subjects, these should include a statement about how the subject’s name and contact information were obtained. No sensitive information about the person (such as a diagnosis of a medical condition) should be included in the letter. The text of these letters and emails must be uploaded to *Zipline* (i.e., a description will not suffice).**

HSD encourages researchers to consider uploading descriptions of most recruitment and screening materials instead of the materials themselves. The goal is to provide the researchers with the flexibility to change some information on the materials without submitting a Modification for IRB approval of the changes. Examples:

- Provide a list of talking points that will be used for phone or in-person conversations instead of a script.
- For the description of a flyer, include the information that it will provide the study phone number and the name of a study contact person (without providing the actual phone number or name). This means that a Modification would not be necessary if/when the study phone number or contact person changes. Also, instead of listing the inclusion/exclusion criteria, the description below might state that the flyer will list one or a few of the major inclusion/exclusion criteria.
- For the description of a video or a website, include a description of the possible visual elements and a list of the content (e.g., study phone number; study contact person; top three inclusion/exclusion criteria; payment of \$50; study name; UW researcher).

**4.3 Relationship with participant population.** Do any members of the study team have an existing relationship with the study population(s)?

Examples: a study team member may have a dual role with the study population (for example, being their clinical care provider, teacher, laboratory director or tribal leader in addition to recruiting them for his/her research).

☒

No

☐

Yes

→ If yes, describe the nature of the relationship.

**4.4 Payment to participants.** The IRB must evaluate subject payment for the possibility that it will unduly influence subjects to participate. Refer to [GUIDANCE Subject Payment](#) when designing subject payment plans. Provide the following information about your plans for paying research subjects in the text box below or note that the information can be found in the consent form.

- The total amount/value of the payment
- Schedule/timing of the payment [i.e., when will subjects receive the payment(s)]
- Purpose of the payment [e.g., reimbursement, compensation, incentive]
- Whether payment will be “pro-rated” so that participants who are unable to complete the research may still receive some part of the payment

The IRB expects the consent process or study information provided to the subjects to include all of the above-listed information about payment, including the number and amount of payments, and especially when subjects can expect to receive payment. One of the most frequent complaints received by HSD is from subjects who expected to receive cash or a check on the day that they completed a study and who were angry or disappointed when payment took 6-8 weeks to reach them.

Participants will receive \$80-\$100 in total for participation in the entire study. Subjects will be compensated at \$20 an hour, rounding up at the half hour mark. This payment compensation will be granted within 1-3 weeks of the study visit date and will be sent as a Tango gift card link to the participant through email. The \$80-\$100 total payment reflects reimbursement for non-car-related travel (as parking in our designated lab parking spot will be covered by the study) as well as compensation for the time and burden of research participation. Those who complete only a portion of the study or are found to be ineligible during the study visit will also be paid based on a pro-rated basis of \$20/hour, which they will receive within 1-3 weeks from their visit. Pilot participants will be compensated the same rate as typical participants.

- 4.5 Non-monetary compensation.** Describe any non-monetary compensation that will be provided. Example: extra credit for students; a toy for a child. If class credit will be offered to students, there must be an alternate way for the students to earn the extra credit without participating in the research.

At the investigator's discretion, participants may also receive copies of their brain images.

**4.6 Will data or specimens be accessed or obtained for recruiting and screening procedures prior to enrollment?**

*Examples: names and contact information; the information gathered from records that were screened; results of screening questionnaires or screening blood tests; Protected Health Information (PHI) from screening medical records to identify possible subjects.*

☐

No

→ If no, skip the rest of this section; go to [question 5.1](#).

☒

Yes

→ If yes, describe the data and/or specimens (including PHI) and whether it will be retained as part of the study data.

We will retain the names and contact information of prospective participants. If prospective participants are screened by phone, results of the phone screening interview will also be retained.

**4.7 Consent for recruiting and screening.** Will consent be obtained for any of the recruiting and screening procedures? ([Section 8: Consent of Adults](#) asks about consent for the main study procedures).

*"Consent" includes: consent from individuals for their own participation; parental permission; assent from children; consent from a legally authorized representative for adult individuals who are unable to provide consent.*

*Examples:*

- *For a study in which names and contact information will be obtained from a registry: the registry should have consent from the registry participants to release their names and contact information to researchers.*
- *For a study in which possible subjects are identified by screening records: there will be no consent process.*
- *For a study in which individuals respond to an announcement and call into a study phone line: the study team person talking to the individual may obtain non-written consent to ask eligibility questions over the phone.*

☐

No

→ If no, skip the rest of this section; go to [question 5.1](#).

☒

Yes

→ If yes, describe the consent process.

A trained member of the study staff who will receive emails and phone calls from potentially interested research participants will obtain non-written consent to ask eligibility questions over the phone during the initial screening process.

**a. Documentation of consent.** Will a written or verifiable electronic signature from the subject on a consent form be used to document consent for the **recruiting and screening procedures**?

☒

No

→ If no, describe the information that will be provided during the consent process and for which procedures.

Potentially eligible participants who contact the study team will set up an initial phone screening interview with a trained member of the study staff. During the phone interview, they will be informed about the main research question being investigated in the study and the study procedures. Should participants pass the initial phone screening interview, they will provide non-written verbal consent to provide their full name and contact information for their preferred method of contact in study records to arrange for formal in-person study visits.

<input type="checkbox"/>	Yes, written	→ If yes, and a <b>written</b> signature will be used to document consent: <ul style="list-style-type: none"> <li>• Upload the consent form to <b>Zipline</b>.</li> </ul>
<input type="checkbox"/>	Yes, electronic	→ If yes, and an <b>electronic</b> signature will be used to document consent: <ul style="list-style-type: none"> <li>• Upload the consent form to <b>Zipline</b>.</li> <li>• <b>If the eSignature process or method for recruiting and screening is different than for the main study procedures</b>, use the questions about electronic consent in Section 8.3 and 8.4 to differentiate between recruiting/screening and main study electronic consent. <b>If electronic consent will be used for recruiting/screening but not main study consent</b>, use 8.3 and 8.4 to describe eConsent and note that it is only for recruiting/screening.</li> </ul>

## 5 PROCEDURES

- 5.1 Study procedures.** Using lay language, provide a complete description of the study procedures, including the sequence, intervention or manipulation (if any), drug dosing information (if any), blood volumes and frequency of draws (if any), use of records, time required, and setting/location. If it is available: Upload a study flow sheet or table to **Zipline**.

*For studies comparing standards of care: It is important to accurately identify the research procedures. See UW IRB [POLICY Risks of Harm from Standard Care](#) and the draft guidance from the federal Office of Human Research Protections, [“Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care”](#); October 20, 2014.*

*Information about pediatric blood volume and frequency of draws that would qualify for expedited review can be found in this [reference table](#) on the Seattle Children’s IRB website.*

The current study will involve an initial phone screening interview, and one 4-5 hour in-person study visit.

1. Initial phone screening interview: The phone screen interview will take approximately 20-30 minutes to complete. Participants will be assessed for major eligibility criteria, including age, sex, mood and mental health history to assess current and past history of SAD, medical history and current medications, and contraindications to oxytocin and MRI. For females to participate, they must also be willing to attend the study visit within the first 10 days of their menstrual cycle (early follicular phase), as mid-cycle hormones have been reported to attenuate extinction recall (Milad et al., 2006).

2. Study Visit: This in-person study visit will take approximately 4-5 hours and involves:

- Written informed consent
- Diagnostic evaluation using the Mini International Neuropsychiatric Interview (MINI)
- Self-report questionnaires
- Drug randomization to receive oxytocin or placebo nasal spray and drug administration\*
- 1-hour MRI scanning session with psychophysiological setup for measuring skin conductance responses (SCR)
- Social learning task (3 phases)
  - Phase 1: Acquisition (completed during mock scan and before drug administration)
  - Phase 2: Extinction (completed after drug administration and with fMRI and SCR)
  - Phase 3: Reinstatement (completed after drug administration and with fMRI and SCR)
- Debriefing

Overall Procedure: Potentially eligible participants who pass the initial phone screening interview will be invited for an in-person study visit at the UW Center of Neuroscience, Neuroendocrinology, and Clinical Translation (CoNNeCT Lab) in Kincaid Hall. A trained member of the study staff (e.g., PI, graduate student clinician) will obtain informed consent (documented in REDCap) after describing the research objectives and potential risks associated with participation. Participants will have an opportunity to ask questions before providing consent. Consented participants will first undergo a urine drug screening test and urine pregnancy test (if female). Should participants prefer to wait to provide a urine sample, they will be given the option to provide the sample after the diagnostic interview. If any test results are positive, participants will be deemed ineligible and will be compensated \$20 for their time. However, if any participant tests positive for cannabis and reports being an infrequent user (e.g., did not screen positive for substances in the phone screen), they will be allowed to participate in the study at a later time as a new participant. If results are negative and participants are still eligible, they will complete the MR Screen form to screen for any MRI contraindications. They will then undergo a diagnostic evaluation using the MINI and review current and recent medications and therapies to confirm study eligibility. Participants will then complete a brief battery of self-report measures assessing demographic information, depression, anxiety, and stress, attachment orientation, social anxiety symptom severity, trait self-focused attention, hormonal status, childhood trauma, and handedness. Participants will then undergo a mock scan while performing Phase 1 “Acquisition” of the social learning task. After completing Phase 1 of the task, participants will walk with the study research assistant to the University of Washington Medical Center Translational Research Unit (5-10 min from Kincaid), where nursing staff will obtain vitals before and after drug administration. Those who are eligible will be randomized to receive either the active oxytocin nasal spray or a matching placebo nasal spray\*. A study nurse will assist in the self-administration of the assigned nasal spray (either oxytocin or placebo) using a standardized administration protocol involving 1 puff per nostril for a total dose of 24 international units (IU). Approval for the experimental use of oxytocin will be provided under an Investigational New Drug (IND) application from the FDA (IND#158017). Nursing staff will monitor patients for adverse events and research staff will monitor patients for acute suicidal ideation immediately after drug administration. Acute suicidal ideation will be assessed using the “Suicide Risk Assessment” form in the attachments. Thereafter, the study research assistant will walk with the participant back to the Kincaid building to undergo Phase 2 and 3 of the social learning task (while undergoing fMRI and recording SCR data). The research assistant will initiate a 3-minute baseline period before starting Phase 2 of the task to collect standardized baseline skin conductance data in the fMRI environment. Participants will complete the MRI scan at the Center for Human Neuroscience (CHN) in Kincaid Hall. Upon completion of the scan, participants will be debriefed about the study and asked to complete four more self-report questionnaires. Two will assess their beliefs about the drug they received and their experience during the fMRI scan, and two will assess their understanding of the CS-US contingencies and their feelings about the task video demonstrator.

Clinician-Rated and Self-Report Measures:

- Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998): The MINI is a brief structured diagnostic interview to assess DSM-5 psychiatric disorders. It takes only approximately 15-30 min to complete and has been shown to have strong validity and reliability in clinical trials.
- Eligibility Form: This clinician-administered measure will be developed specifically for the purposes of this study to assess demographic information, and to document other inclusion and exclusion criteria (e.g., medical illnesses, nasal pathology, suicidal/homicidal ideation, cigarette use, concurrent medications, steroid use, urine pregnancy/drug screening test results).

- Medication and Therapy Form: This measure was developed specifically for the purposes of this study. The purpose of this form is to screen for and collect data on any past or concomitant medications or behavioral therapies.
- Demographic Questionnaire: This measure will be developed specifically for the purposes of this study to assess demographic information.
- Liebowitz Social Anxiety Scale- self-report (LSAS-SR; Baker et al., 2002; Liebowitz, 1987): The LSAS is a 24-item self-report instrument that assesses fear and avoidance of social situations in the past week. It is widely used in treatment studies for SAD. The LSAS has been validated in clinical samples and has high internal consistency ( $\alpha = .82-.92$ ) (Heimberg et al., 1999).
- Depression Anxiety Stress Scale-21 (DASS; Lovibond & Lovibond, 1995): The DASS is a shortened, 21-item version of the original DASS self-report questionnaire designed to measure dimensional aspects of depression, anxiety, and stress.
- Experience in Close Relationships Inventory (ECR; Brennan et al., 1998): The ECR is a 36-item self-report questionnaire that measures attachment anxiety and avoidance in adults. It yields two subscales reflecting attachment anxiety (anxiety about being rejected or abandoned) and attachment avoidance (discomfort with closeness and intimacy).
- Self-Consciousness Scale Revised (SCS-R; Scheier & Carver, 1985): The SCS-R is a measure of trait self-focused attention and will be assessed as a potential moderator of oxytocin's effects.
- Hormone Questionnaire: This questionnaire is designed to assess hormonal status of participants and includes questions about gender identity, menstruation, and use of hormones including oral contraception.
- Child Trauma Questionnaire (CTQ; Bernstein, 1995): The CTQ- Short Form is a 28-item questionnaire that assesses traumatic experiences during childhood.
- Edinburgh Handedness Inventory (EHI; Oldfield, 1971): This questionnaire is given to assess handedness to determine whether it differs between groups or as a potential moderator of fMRI data.
- MR Screen Form: This is a brief questionnaire that assesses all of the contraindications to MRI and will be used during the initial phone screening and in-person screening evaluation.
- Suicide Risk Assessment: This is a brief 1-page assessment designed to screen for suicidal ideation based on presence, frequency, and intensity of thoughts, as well as suicidal intent and plans. The assessment will be used by research coordinators during the phone screen interview and again by research staff after drug administration to screen for suicidal ideation.
- Adverse Events Form: This self-report form will be administered after nasal spray administration to assess for adverse events. Participants will be asked to report on a symptom checklist whether they experienced a negative reaction to the nasal spray. If participants endorse "yes" on any item, a study nurse will monitor them immediately after nasal spray administration and the study research assistant will follow up with the participant to ask whether the symptom resolves by the end of the study visit.
- Assessment of Blind Questionnaire: This questionnaire will be given at the end of the study visit to assess for participants' expectancies regarding the drug they received. Participants will be asked which nasal spray they believe they received (oxytocin or placebo), their degree or certainty, and to describe their reasons why.
- MRI Exit Questionnaire: This measure will assess participants' overall experience in the scanner and ask questions regarding their overall emotional state during the scan and symptom-specific thoughts during the scan.

- CS-US Contingency Questionnaire: This brief questionnaire will assess whether the participant understood the conditioned stimuli contingencies by asking if they can recall which images were associated with a shock.
- Evaluation of the Demonstrator and US: This brief questionnaire will ask about the participants' feelings toward the task video demonstrator, asking about empathy, likeability, discomfort, and believability of the video demonstrator.

Drug Administration: In a randomized, double-blind, placebo-controlled design, participants will receive either 24 IU of intranasal oxytocin (the most commonly studied dose in acute administration protocols) or matching placebo, between 30-45 minutes prior to undergoing fMRI, which reflects oxytocin's predicted maximum physiological effects in neuroimaging studies. The active oxytocin drug is thought to have its peak effects within 30-45 minutes after administration, and maintain behavioral effects through central nervous system activity for up to 90 minutes after administration. Nasal sprays will be obtained by Tonix Pharmaceuticals under an approved IND application (IND#158017). Oxytocin is currently approved by FDA in an intravenous (IV) form for the purpose of helping in childbirth. It is, however, not approved for use in patients with SAD, and a nasal form of the drug is not approved. In this study, the purpose, dose, and manner of administration of oxytocin are considered experimental. The randomization scheme will be stratified by gender identity and be carried out by the Investigational Drug Services research pharmacy upon dispensing. Stratifying by gender identity will enable investigators to examine gender differences in oxytocin's effects, and allow for more meaningful stratification for individuals who identify as non-binary or transgender, compared to randomizing by sex. However, for participants who prefer to not disclose their gender identity, we will perform randomization based on sex assigned at birth, which is a required variable for study inclusion. The study physician will prescribe nasal sprays on a per-patient basis and provide medical oversight regarding reported adverse events and risk coverage for participants enrolled in the study. Participants will follow a standardized protocol for self-administering the metered dose nasal sprays (12 IU oxytocin per spray) (see SOP for Self-Administration of Oxytocin/Placebo Nasal Spray) and the study nurse at the Translational Research Unit will be present for drug administration. Only the Investigational Drug Service research pharmacy will be unblinded to drug condition during the study, as they will be assisting with randomization and maintaining the study blind.\*

\*Pilot subject procedures: Pilot subjects will follow every procedure listed above *except for* the drug randomization and blinding procedures. Pilot subjects will only receive the placebo bottles which Tonix has provided for piloting purposes, removing the need for randomization to drug condition and blinding.

Social Learning Task: The task comprises of 3 phases: Acquisition, Extinction, and Reinstatement. The Acquisition phase will be completed during the mock scan, prior to drug administration and the MRI scan, whereas the Extinction and Reinstatement phases will be completed in the MRI scanner with SCR recordings after drug administration. In each phase, conditioned stimuli (angry faces) will be presented 8 times each in pseudorandomized order. During Acquisition, two angry faces (CS+) will be repeatedly paired with a mild electric shock (unconditioned stimulus, US) and a third angry face (CS-) will never be paired with a shock. Prior to the task, a work-up procedure will be used to calibrate the shock level for each participant in order to find a level that is subjectively uncomfortable, but not painful. Shocks will be incrementally administered through an electrode attached to the participant's wrist until the participant determines the shocks to be "uncomfortable, but not painful." Participants will be asked to rate the experience of the shocks. All study staff will follow the Lab-wide SOP for Safe Use of Experimental Stimulation. During the extinction phase of the task, participants will watch a video of a male demonstrator acting calmly while exposed to non-reinforced presentations of the CS- and to one of the previously reinforced CS+ faces (CS+vic safety) but twitching his arm while exposed to reinforced presentations (75% of the time) of the other CS+ (CS+vic reinf). Having two CS+ cues—one that gets

reinforced and one that does not—allows us to assess the effect of observing the demonstrator experience danger compared to safety. Importantly, participants will never receive any shocks during extinction. During reinstatement, participants will follow a standard reinstatement procedure that involves receiving three unsignalled reminder shocks before being re-exposed to all 3 CSs to test the return of fear. SCR data will be recorded to index learning during each phase of the task.

MRI Scan: Participants will be scanned at the UW CHN in a Siemens MRI 3.0 Tesla PRISMA scanner equipped with a 64-channel head coil. Blood oxygen level dependent (BOLD) fMRI data will be collected using a T2\*-weighted echo planar imaging sequence. A high-resolution T1-weighted MPRAGE structural scan will also be acquired for each participant. Participants will also have their heart rate and respiration monitored using a pulse oximeter on the finger. Participants will also have their eye movements tracked without any further equipment attached to them. Eye movements will be tracked using EyeLink1000 which records gaze position on the screen and pupil size using infrared light.

Debriefing: Participants will complete the Assessment of Blind Questionnaire and an MRI exit questionnaire to assess which drug condition participants think they were assigned to and their reactions to MRI. They will also complete the CS-US Contingency Questionnaire and Evaluation of the Demonstrator and US Questionnaire. During debriefing, they will be given a chance to ask questions about the study. The research assistant will also follow-up on unresolved adverse events that were reported after nasal spray administration at this time.

**5.2 Recordings.** Does the research involve creating audio or video recordings?

- ☐ **No** → If no, go to [question 5.3](#).
- ☒ **Yes** → If yes, verify that you have described what will be recorded in 5.1 and answer question a.
- a. Before recording, will consent for being recorded be obtained from subjects and any other individuals who may be recorded?
- ☐ **No** → If no, email [hsdinfo@uw.edu](mailto:hsdinfo@uw.edu) before submitting this application in Zipline. In the email, include a brief description of the research and a note that individuals will be recorded without their advance consent.
- ☒ **Yes**

**5.3 MRI scans.** Will any subjects have a Magnetic Resonance Imaging (MRI) scan as part of the study procedures?

*This means scans that are performed solely for research purposes or clinical scans that are modified for research purposes (for example, using a gadolinium-based contrast agent when it is not required for clinical reasons).*

- ☐ **No** → If no, go to [question 5.4](#).
- ☒ **Yes** → If yes, answer questions a through c.
- a. **Describe the MRI scan(s).** Specifically:
- What is the purpose of the scan(s)? *Examples: obtain research data; safety assessment associated with a research procedure.*
  - Which subjects will receive an MRI scan?
  - Describe the minimum and maximum number of scans per subject, and over what time period the scans will occur. *For example: all subjects will undergo two MRI scans, six months apart.*
- All subjects will undergo an MRI scan during the in-person study visit, after receiving either oxytocin or placebo.

**b. MRI facility.** At which facility(ies) will the MRI scans occur? Check all that apply.

<input type="checkbox"/>	UWMC Radiology/Imaging Services (the UWMC clinical facility)
<input type="checkbox"/>	DISC Diagnostic Imaging Sciences Center (UWMC research facility)
<input checked="" type="checkbox"/>	CHN Center for Human Neuroscience MRI Center (Arts & Sciences research facility)
<input type="checkbox"/>	BMIC Biomolecular Imaging Center (South Lake Union research facility)
<input type="checkbox"/>	Harborview Radiology/Imaging Services (the Harborview clinical facility)
<input type="checkbox"/>	SCCA Imaging Services
<input type="checkbox"/>	Northwest Diagnostic Imaging
<input type="checkbox"/>	Other: identify in the text box below:

**c. Personnel.** For MRI scans that will be conducted at the DISC, CHN or BMIC research facilities: Indicate who will be responsible for operating the MRI scanner by checking all that apply.

<input checked="" type="checkbox"/>	MRI technician who is formally qualified
<input checked="" type="checkbox"/>	Researcher who has completed scanner operator training provided by a qualified MRI operator

**5.4 Data variables.** Describe the specific data that will be obtained (including a description of the most sensitive items). Alternatively, a list of the data variables may be uploaded to **Zipline**.

#### List of Data Variables

\*denotes sensitive variables

#### Demographic and clinical variables:

1. \*Sex (required for study inclusion criteria)
2. \*Gender identity
3. \*Age
4. \*Use of current medications and therapies
5. \*Past history of medication use and therapy
6. \*Race
7. \*Ethnicity
8. Highest education level completed
9. Handedness (EHI)
10. \*Body weight and height (body mass index)
11. \*Psychiatric status and history using the MINI [which includes current and past primary and comorbid diagnoses, any subthreshold diagnoses, age of onsets for all diagnoses met]
12. \*Social anxiety severity (LSAS)- severity of social anxiety symptoms in various social situations
13. \*Depression, anxiety, and stress (DASS)- levels of depression, anxiety, stress experienced in past week
14. Attachment orientation (ECR)
15. Self-focused attention (SCS-R)
16. Hormone Questionnaire
17. Childhood Trauma Questionnaire (CTQ)
18. Current and past medications

## 19. Current and past therapies

### **Neural/MRI-related outcomes:**

1. Neural activation in regions of interest (amygdala, VMPFC, and hippocampus)
2. Functional connectivity between VMPFC-amygdala and VMPFC-hippocampus
3. Skin conductance responses during social learning task
4. Heart rate and respiration using a pulse oximeter
5. Eye tracking measures (eye movements, pupil dilation) using the EyeLink1000 which is mounted within the MRI scanner
6. Experience during MRI scan [Exit Questionnaire]
7. MRI contraindications [MR Screen Questionnaire]
8. Room temperature in MRI scanning room

### **Other outcomes:**

1. Assessment of blind
2. Adverse events
3. CS-US Contingency Questionnaire
4. Evaluation of the Demonstrator and US Questionnaire

- 5.5 Data sources.** For all types of data that will be accessed or collected for this research: Identify whether the data are being obtained from the subjects (or subjects' specimens) or whether they are being obtained from some other source (and identify the source).

*If you have already provided this information in Question 5.1, you do not need to repeat the information here.*

All sources of data for this study will be obtained from participants. Nursing staff will access participants' electronic medical record (EMR) through EPIC in order to chart the study visit and vital signs. It is possible that nursing staff may need to go into participants' charts in their EMR or access previous records in the EMR in certain situations. For example, if a participant has an adverse reaction to the drug or if the participant exhibits psychotic behavior, other parts of their EMR may be accessed by TRU nurses. Although data from patients' EMR may be briefly reviewed as needed, EMR data will not be systematically examined for participants in the study.

- 5.6 Identifiability of data and specimens.** Answer these questions carefully and completely. This will allow HSD to accurately determine the type of review that is required and the relevant compliance requirements. Review the following definitions before answering the questions:

***Access** means to view or perceive data, but not to possess or record it. See, in contrast, the definition of "obtain".*

***Identifiable** means that the identity of an individual is or may be readily (1) ascertained by the researcher or any other member of the study team from specific data variables or from a combination of data variables, or (2) associated with the information.*

***Direct identifiers** are direct links between a subject and data/specimens. Examples include (but are not limited to): name, date of birth, medical record number, email or IP address, pathology or surgery accession number, student number, or a collection of data that is (when taken together) identifiable.*

***Indirect identifiers** are information that links between direct identifiers and data/specimens. Examples: a subject code or pseudonym.*

***Key** refers to a single place where direct identifiers and indirect identifiers are linked together so that, for example, coded data can be identified as relating to a specific person. Example: a master list that contains the data code and the identifiers linked to the codes.*

***Obtain** means to possess or record in any fashion (writing, electronic document, video, email, voice recording, etc.) for research purposes and to retain for any length of time. This is different from **accessing**, which means to view or perceive data.*

a. Will you or any members of your team have access to any direct or indirect identifiers?

☒ Yes

→ If yes, describe which identifiers and for which data/specimens.

Research participants will be given a unique study identifier associated with their data. Identifying information obtained during the phone screening process (e.g., demographic information, name, and contact information) will be kept in a separate password-protected file stored on a secure internal server.

☐ No

→ If no, select the reason(s) why you (and all members of your team) will not have access to direct or indirect identifiers.

☐ There will be no identifiers.

☐ Identifiers or the key have been (or will have been) destroyed before access.

☐ There is an agreement with the holder of the identifiers (or key) that prohibits the release of the identifiers (or key) to study team members under any circumstances.

*This agreement should be available upon request from the IRB. Examples: a Data Use Agreement, Repository Gatekeeping form, or documented email.*

☐ There are written policies and procedures for the repository/database/data management center that prohibit the release of the identifiers (or identifying link). This includes situations involving an Honest Broker.

☐ There are other legal requirements prohibiting the release of the identifiers or key. Describe them below.

b. Will you or any study team members obtain any direct or indirect identifiers?

☒ Yes

→ If yes, describe which identifiers and for which data/specimens.

Yes, the study research assistant will use indirect identifiers corresponding to a code assigned to each subject who participates in the study. The study research assistant will only obtain participants' full name and detailed contact information for those who pass the initial phone screening interview to coordinate study visits.

☐ No

→ If no, select the reason(s) why you (and all members of your team) will not obtain direct or indirect identifiers.

☐ There will be no identifiers.

☐ Identifiers or the key have been (or will have been) destroyed before access.

☐ There will be an agreement with the holder of the identifiers (or key) that prohibits the release of the identifiers (or key) under any circumstances.

*This agreement should be available upon request from the IRB. Examples: a Data Use Agreement, Repository Gatekeeping form, or documented email.*

☐ There are written policies and procedures for the repository/database/data management center that prohibit the release of the identifiers (or identifying link). This includes situations involving an Honest Broker.

☐ There are other legal requirements prohibiting the release of the identifiers or key. Describe them below.

c. If any identifiers will be obtained, indicate how the identifiers will be stored (and for which data). NOTE: Do not describe the data security plan here – that information is requested in section 9.6.

☐ Identifiers will be stored with the data. Describe the data to which this applies:

☒ Identifiers and study data will be stored separately but a link will be maintained between the identifiers and the study data (for example, through the use of a code). Describe the data to which this applies:

Screening data; study data. A unique study identifier corresponding to each participant in the study will be used and stored in the screening/enrollment log saved on a HIPAA-compliant server for the Fang Lab.

☐ Identifiers and study data will be stored separately, with no link between the identifiers and the study data. Describe the data to which this applies:

d. **Research collaboration.** Will individuals who provide coded information or specimens for the research also collaborate on other activities for this research? If yes, identify the activities and provide the name of the collaborator's institution/organization.

*Examples include but are not limited to: (1) study, interpretation, or analysis of the data that results from the coded information or specimens; and (2) authorship on presentations or manuscripts related to this work.*

Drs. Armita Golkar and Andreas Olsson from the Karolinska Institutet in Sweden will serve as external collaborators on this project. They have developed and tested the task which we are using in the study, and will be assisting with data processing, analysis, and interpretation. They will also assist with conference presentations and manuscripts from this work. They will only need access to de-identified data for our collaboration.

**5.7 Protected Health Information (PHI).** Will participants' identifiable PHI be accessed, obtained, used, or disclosed for any reason (for example, to identify or screen potential subjects, to obtain study data or specimens, for study follow-up) that does not involve the creation or obtaining of a Limited Data Set?

*PHI is individually identifiable healthcare record information or clinical specimens from an organization considered a "covered entity" by federal HIPAA regulations, in any form or media, whether electronic, paper, or oral. You must answer yes to this question if the research involves identifiable health care records (e.g., medical, dental, pharmacy, nursing, billing, etc.), identifiable healthcare information from a clinical department repository, or observations or recordings of clinical interactions.*

☐ **No** → If no, skip the rest of this question; [go to question 5.8](#)

☒ **Yes** → If yes, answer all of the questions below.

**a.** Describe the PHI and the reason for using it. *Be specific. For example, will any "free text" fields (such as physician notes) be accessed, obtained, or used?*

However, given that participants will need to be registered with an MRN as patients in the UWMC EMR system, it is possible that the study nurse at the Translational Research Unit may review medical and psychiatric information included in participants' chart during the study visit as needed.

**b.** Is any of the PHI located in Washington State?

☐ **No**

☒ **Yes**

**c.** Describe the pathway of how the PHI will be accessed or obtained, starting with the source/location and then describing the system/path/mechanism by which it will be identified, accessed, and copied for the research. *Be specific. For example: directly view records; search through a department's clinical database; submit a request to Leaf.*

PHI may be accessed by study nurses at the Translational Research Unit prior to drug administration by directly viewing records.

**d.** For which PHI will subjects provide HIPAA authorization before the PHI is accessed, obtained and/or used?

Participants will provide HIPAA authorization for study nurses at the Translational Research Unit to access their name, MRN, and medical and psychiatric health information in their chart.

Confirm by checking the box that the UW Medicine [HIPAA Authorization](#) form maintained on the HSD website will be used to access, obtain, use, or disclose any UW Medicine PHI.

☒ **Confirmed**

e. Will you obtain any HIPAA authorizations electronically (i.e., e-signature)?

☐ No  
☒ Yes

If 'Yes', confirm by checking the box that you have read and understand the 'Special Considerations' section of the [GUIDANCE Electronic Informed Consent](#) for information regarding the use of electronic signatures and HIPAA authorizations.

☒ Confirmed

f. For which PHI will HIPAA authorization NOT be obtained from the subjects?

Provide the following assurances by checking the boxes.

☒ The minimum necessary amount of PHI to accomplish the purposes described in this application will be accessed, obtained and/or used.

☒ The PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.

☒ The HIPAA "accounting for disclosures" requirement will be fulfilled, if applicable. See [UW Medicine Compliance Policy #104](#).

☒ There will be reasonable safeguards to protect against identifying, directly or indirectly, any patient in any report of the research.

**5.8 Genomic data sharing.** Will the research obtain or generate genomic data?

☒ No  
☐ Yes → If yes, answer the question below.

a. Will genomic data from this research be sent to a national database (for example, NIH's dbGaP database)?

☐ No  
☐ Yes → If yes, complete the [SUPPLEMENT Genomic Data Sharing](#) and upload it to **Zipline**.

**5.9 Whole genome sequencing.** For research involving biospecimens: Will the research include whole genome sequencing?

*Whole genome sequencing is sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen.*

☒ No  
☐ Yes

**5.10 Possible secondary use or sharing of information, specimens, or subject contact information.** Is it likely that the obtained or collected information, specimens, or subject contact information will be used for any of the following:

- Future research not described in this application (in other words, secondary research)
- Submission to a repository, registry, or database managed by the study team, colleagues, or others for research purposes
- Sharing with others for their own research

**Please consider the broadest possible future plans and whether consent will be obtained now from the subjects for future sharing or research uses** (which it may not be possible to describe in detail at this time).

Answer **YES** even if future sharing or uses will use de-identified information or specimens. Answer **NO** if sharing is unlikely or if the only sharing will be through the NIH Genomic Data Sharing described in question 5.8.

*Many federal grants and contracts now require data or specimen sharing as a condition of funding, and many journals require data sharing as a condition of publication. "Sharing" may include (for example): informal arrangements to share banked data/specimens with other investigators; establishing a repository that will formally share with other researchers through written agreements; or sending data/specimens to a third party repository/archive/entity such as the Social Science Open Access Repository (SSOAR), or the UCLA Ethnomusicology Archive.*

☐

No

☒

Yes → If yes, answer all of the questions below.

a. Describe what will be stored for future use, including whether any direct or indirect (e.g., subject codes) identifiers will be stored.

All participant data will be stored for future use on the internal lab server, including indirect study identifiers as well as the password-protected file containing direct identifiers (e.g., name, contact info) of study participants.

b. Describe what will be shared with other researchers or with a repository/database/registry, including whether direct identifiers will be shared and (for specimens) what data will be released with the specimens.

Direct identifiers will not be shared with other researchers/repositories.

c. Who will oversee and/or manage the sharing?

The PI of the study, Dr. Angela Fang, will oversee and manage data sharing.

d. Describe the possible future uses, including limitations or restrictions (if any) on future uses or users. As stated above, consider the broadest possible uses.

*Examples: data will be used only for cardiovascular research; data will not be used for research on population origins.*

Possible future uses of data from this study include combining deidentified data with previous deidentified data from other studies, either within our lab or with outside collaborators, as well as including deidentified data from this study into a large data repository in our lab.

e. Consent. Will consent be obtained now from subjects for the secondary use, banking and/or future sharing?

☐ No  
☒ Yes

→ If yes, be sure to include the information about this consent process in the consent form (if there is one) and in the answers to the consent questions in [Section 8](#).

f. Withdrawal. Will subjects be able to withdraw their data/specimens from secondary use, banking or sharing?

☐ No  
☒ Yes

→ If yes, describe how, and whether there are any limitations on withdrawal.

*Example: data can be withdrawn from the repository but cannot be retrieved after they are released.*

Subjects will be informed during the consent process that they can opt out of the possible submission of their data to a repository. Subjects can also withdraw their data for secondary use at any time by notifying a member of the research team who will withdraw the data.

g. Agreements for sharing or release. Confirm by checking the box that the sharing or release will comply with UW (and, if applicable, UW Medicine) policies that require a formal agreement with the recipient for release of data or specimens to individuals or entities other than federal databases.

*Data Use Agreements or Gatekeeping forms are used for data; Material Transfer Agreements are used for specimens (or specimens plus data). Do not attach any template agreement forms; the IRB neither reviews nor approves them*

☒ Confirmed

**5.11 Communication with subjects during the study.** Describe the types of communication (if any) the research team will have with already-enrolled subjects during the study. Provide a description instead of the actual materials themselves.

*Examples: email, texts, phone, or letter reminders about appointments or about returning study materials such as a questionnaire; requests to confirm contact information.*

Participants will first contact the study research assistant via phone or email, and will be contacted via phone call for initial screening. Once enrolled, participants may be contacted through email or phone to coordinate study appointments through their preferred method of contact.

**5.12 Future contact with subjects.** Is there a plan to retain any contact information for subjects so that they can be contacted in the future?

☐

No

☒

Yes

→ If yes, describe the purpose of the future contact, and whether use of the contact information will be limited to the study team; if not, describe who else could be provided with the contact information. Describe the criteria for approving requests for the information.

*Examples: inform subjects about other studies; ask subjects for additional information or medical record access that is not currently part of the study proposed in this application; obtain another sample.*

Yes, participants will be asked whether they would like to be added to a research registry for the lab which will include collecting contact information to be used and accessed only by members of the study team for future research participation.

**5.13 Alternatives to participation.** Are there any alternative procedures or treatments that might be advantageous to the subjects?

*If there are no alternative procedures or treatments, select "No". Examples of advantageous alternatives: earning extra class credit in some time-equivalent way other than research participation; obtaining supportive care or a standard clinical treatment from a health care provider instead of participating in research with an experimental drug.*

☐

No

☒

Yes

→ If yes, describe the alternatives.

Clinical participants may seek clinical evaluation through other means than in this study. Treatment will not be provided in this study, as oxytocin is not a recommended treatment for SAD.

**5.14 Upload to Zipline** all data collection forms (if any) that will be directly used by or with the subjects, and any scripts/talking points that will be used to collect the data. Do not include data collection forms that will be used to abstract data from other sources (such as medical or academic records), or video recordings.

- **Examples:** survey, questionnaires, subject logs or diaries, focus group questions.
- **NOTE:** Sometimes the IRB can approve the general content of surveys and other data collection instruments rather than the specific form itself. This prevents the need to submit a modification request for future minor changes that do not add new topics or increase the sensitivity of the questions. To request this general approval, use the text box below to identify the questionnaires/surveys/ etc. for which you are seeking this more general approval. Then briefly describe the scope of the topics that will be covered and the most personal and sensitive questions. The HSD staff person who screens this application will let you know whether this is sufficient or whether you will need to provide more information.
- **For materials that cannot be uploaded:** upload screenshots or written descriptions that are sufficient to enable the IRB to understand the types of data that will be collected and the nature of the experience for the participant. You may also provide URLs (website addresses) or written descriptions below. Examples of materials that usually cannot be uploaded: mobile apps; computer-administered test; licensed and restricted standardized tests.
- **For data that will be gathered in an evolving way:** This refers to data collection/questions that are not pre-determined but rather are shaped during interactions with participants in response to observations and responses made during those interactions. If this applies to the proposed research, provide a description of the process by which the data collection/questions will be established during the interactions with subjects, how the data collection/questions will be documented, the topics likely to be addressed, the most sensitive type of information likely to be gathered, and the limitations (if any) on topics that will be raised or pursued.

Use this text box (if desired) to provide:

- Short written descriptions of materials that cannot be uploaded, such as URLs
- A description of the process that will be used for data that will be gathered in an evolving way.
- The general content of questionnaires, surveys and similar instruments for which general approval is being sought. (See the **NOTE** bullet point in the instructions above.)

We would like to obtain general approval to use the following clinical instruments and self-report measures in the study:

- Eligibility Form: This clinician-administered measure will be developed specifically for the purposes of this study to assess demographic information, and to document other inclusion and exclusion criteria (e.g., medical illnesses, nasal pathology, suicidal/homicidal ideation, cigarette use, concurrent medications, steroid use, urine pregnancy/drug screening test results).
- Demographic Questionnaire: This measure will be developed specifically for the purposes of this study to assess demographic information.
- Adverse Events Form: This self-report form will be administered after nasal spray administration to assess for adverse events. Participants will be asked to report on a symptom checklist whether they experienced a negative reaction to the nasal spray. If participants endorse “yes” on any item, a study nurse will monitor them immediately after nasal spray administration and the study research assistant will follow up with the participant to ask whether the symptom resolves by the end of the study visit.
- Assessment of Blind Questionnaire: This questionnaire will be given at the end of the study visit to assess for participants’ expectancies regarding the drug they received. Participants will be asked which nasal spray they believe they received (oxytocin or placebo), their degree or certainty, and to describe their reasons why.
- MRI Exit Questionnaire: This measure will assess participants’ overall experience in the scanner and ask questions regarding their overall emotional state during the scan and symptom-specific thoughts during the scan.

We have uploaded the following instruments and measures for IRB approval:

- Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998): The MINI is a brief structured diagnostic interview to assess DSM-5 psychiatric disorders. It takes only approximately 30 min to complete and has been shown to have strong validity and reliability in clinical trials.
- Liebowitz Social Anxiety Scale- Self Report (LSAS-SR; Baker et al., 2002; Liebowitz, 1987): The LSAS is a 24-item self-report instrument that assesses fear and avoidance of social situations in the past week. It is widely used in treatment studies for SAD. The LSAS has been validated in clinical samples and has high internal consistency ( $\alpha = .82-.92$ ) (Heimberg et al., 1999).
- Medication and Therapy Form: This measure was developed specifically for the purposes of this study. The purpose of this form is to screen for and collect data on any past or concomitant medications or behavioral therapies.
- Depression Anxiety Stress Scale-21 (DASS; Lovibond & Lovibond, 1995): The DASS is a shortened, 21-item version of the original DASS self-report questionnaire designed to measure dimensional aspects of depression, anxiety, and stress.
- Experience in Close Relationships Inventory (ECR; Brennan et al., 1998): The ECR is a 36-item self-report questionnaire that measures attachment anxiety and avoidance in adults. It yields two subscales reflecting attachment anxiety (anxiety about being rejected or abandoned) and attachment avoidance (discomfort with closeness and intimacy).
- Self-Consciousness Scale Revised (SCS-R; Scheier & Carver, 1985): The SCS-R is a measure of trait self-focused attention and will be assessed as a potential moderator of oxytocin’s effects.
- Edinburgh Handedness Inventory (EHI; Oldfield, 1971): This questionnaire is given to assess handedness to determine whether it differs between groups or as a potential moderator of fMRI data.

- Hormone Questionnaire: This questionnaire is given to assess hormonal status in order to investigate whether hormones play a role in social learning.
- Child Trauma Questionnaire (CTQ; Bernstein, 1995): This measure is used to assess a range of traumatic experiences in childhood in order to investigate whether early life trauma impairs social learning.
- MR Screen Form: This is a brief questionnaire that assesses all of the contraindications to MRI provided by the CHN that will be completed prior to each scan. These questions will also be asked on the REDCap prescreen to screen for any MRI contraindications.
- CS-US Contingency Questionnaire: This brief questionnaire will assess whether the participant understood the conditioned stimuli contingencies by asking if they can recall which images were associated with a shock.
- Evaluation of the Demonstrator and US: This brief questionnaire will ask about the participants' feelings toward the task video demonstrator, asking about empathy, likeability, discomfort, and believability of the video demonstrator.

**5.15 SARS-CoV-2 testing.** Will the subjects be tested for the SARS-CoV-2 coronavirus?

*If the only testing is to screen the subjects (question 2.8), you do not need to answer this question*

☒ No  
☐ Yes

→ If yes:

- Name the testing lab
- Confirm that the lab and its use of this test is CLIA-certified or certified by the Washington State Department of Health
- Describe whether you will return the results to the participants and, if yes, who will do it and how (including any information you would provide to subjects with positive test results).

**5.16 Research equipment and COVID-19.** Does your research involve any equipment that will be used on more than one subject that is not part of a clinical facility?

*Examples: a computer tablet, a portable research ultra-sound device).*

☐ No  
☒ Yes

→ If yes: confirm by checking the box below that the disinfection and cleaning of the equipment will meet the enhanced UW Environmental Health & Safety requirements described here:

<https://www.ehs.washington.edu/system/files/resources/cleaning-disinfection-protocols-covid-19.pdf>

☒ Confirmed

## 6 CHILDREN (MINORS) and PARENTAL PERMISSION

### 6.1 Involvement of minors. Does the research include minors (children)?

**Minor or child** means someone who has not yet attained the legal age for consent for the research procedures, as described in the applicable laws of the jurisdiction in which the research will be conducted. This may or may not be the same as the definition used by funding agencies such as the National Institutes of Health.

- In Washington State the generic age of consent is 18, meaning that anyone under the age of 18 is considered a child.
- There are some procedures for which the age of consent is much lower in Washington State.
- The generic age of consent may be different in other states, and in other countries.

☒ **No** → If no, go to [Section 8](#).

☐ **Yes** → If yes, provide the age range of the minor subjects for this study and the legal age for consent in the study population(s). If there is more than one answer, explain.

☐ **Don't know** → This means it is not possible to know the age of the subjects. For example, this may be true for some research involving social media, the Internet, or a dataset that is obtained from another researcher or from a government agency. Go to [Section 8](#).

**6.2 Parental permission.** Parental permission means actively obtaining the permission of the parents. This is not the same as “passive” or “opt out” permission where it is assumed that parents are allowing their children to participate because they have been provided with information about the research and have not objected or returned a form indicating they don’t want their children to participate.

a. Will parental permission be obtained for:

☐ All of the research procedures → Go to [question 6.2b](#).

☐ None of the research procedures → Use the table below to provide justification, and skip question 6.2b.

☐ Some of the research procedures → Use the table below to identify the procedures for which parental permission will not be obtained.

*Be sure to consider all research procedures and plans, including screening, future contact, and sharing/banking of data and specimens for future work.*

Children Group <sup>1</sup>	Describe the procedures or data/specimen collection (if any) for which there will be NO parental permission <sup>2</sup>	Reason why parental permission will not be obtained	Will parents be informed about the research? <sup>3</sup>	
			YES	NO
			<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>

Document Date & Version

04/29/2021

Version 3.3

APPLICATION IRB Protocol

Researcher Date & Version

9/13/2024

Version 9.0

Page 35 of 64

<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

#### Table footnotes

1. If the answer is the same for all children groups or all procedures: collapse the answer across the groups and/or procedures.
2. If identifiable information or biospecimens will be obtained without parent permission, any waiver granted by the IRB does not override parents' refusal to provide broad consent (for example, through the Northwest Biotrust).
3. Will parents be informed about the research beforehand even though active permission is not being obtained?

**b. Indicate the plan for obtaining parental permission. One or both boxes must be checked.**

- ☐ Both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available; or when only one parent has legal responsibility for the care and custody of the child
- ☐ One parent, even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

*This is all that is required for minimal risk research.*

If both boxes are checked, explain:

**6.3 Children who are wards.** Will any of the children be wards of the State or any other agency, institution, or entity?

☐ No  
☐ Yes

→ If yes, an advocate may need to be appointed for each child who is a ward. The advocate must be in addition to any other individual acting on behalf of the child as guardian or in loco parentis. The same individual can serve as advocate for all children who are wards.

Describe who will be the advocate(s). The description must address the following points:

- Background and experience
- Willingness to act in the best interests of the child for the duration of the research
- Independence of the research, research team, and any guardian organization

**6.4 UW Office for Youth Programs Development and Support.** If the project involves interaction (in-person or remotely) with individuals under the age of 18, researchers must comply with **UW Administrative Policy Statement 10.13** and the requirements listed at [this website](#). This includes activities that are deemed to be Not Research or Exempt. It does not apply to third-party led research (i.e., research conducted by a non-UW PI). [Information and FAQs](#) for researchers are available.

**This point is advisory only; there is no need to provide a response.**

## 7 ASSENT OF CHILDREN (MINORS)

Go to [Section 8](#) if your research does not involve children (minors).

**7.1 Assent of children (minors).** Though children do not have the legal capacity to “consent” to participate in research, they should be involved in the process if they are able to “assent” by having a study explained to them and/or by reading a simple form about the study, and then giving their verbal choice about whether they want to participate. They may also provide a written assent if they are older. See [WORKSHEET Children](#) for circumstances in which a child’s assent may be unnecessary or inappropriate.

a. Will assent be obtained for:

- |  |   |
|--|---|
| <input type="checkbox"/> All research procedures and child groups          | → Go to <a href="#">question 7.2</a> .  |
| <input type="checkbox"/> None of the research procedures and child groups  | → Use the table below to provide justification, then skip to <a href="#">question 7.6</a> |
| <input type="checkbox"/> Some of your research procedures and child groups | → Use the table below to identify the procedures for which assent will not be obtained.   |

*Be sure to consider all research procedures and plans, including screening, future contact, and sharing/banking of data and specimens for future work.*

Children Group <sup>1</sup>	Describe the procedures or data/specimen collection (if any) for which assent will NOT be obtained	Reason why assent will not be obtained

### Table footnotes

1. If the answer is the same for all children groups or all procedures, collapse your answer across the groups and/or procedures.

**7.2 Assent process.** Describe how assent will be obtained, for each child group. If the research involves children of different ages, answer separately for each group. If the children are non-English speakers, include a description of how their comprehension of the information will be evaluated.

**7.3 Dissent or resistance.** Describe how a child’s objection or resistance to participation (including non-verbal indications) will be identified during the research, and what the response will be.

**7.4 E-consent.** Will any electronic processes (email, websites, electronic signatures, etc.) be used to present assent information to subjects/and or to obtain documentation (signatures) of assent? If yes, describe how this will be done.

**7.5 Documentation of assent.** Which of the following statements describes whether documentation of assent will be obtained?

- ☐ None of the research procedures and child groups
- Use the table below to provide justification, then go to [question 7.5.b](#)
- ☐ All of the research procedures and child groups
- Go to [question 7.5.a](#), do not complete the table
- ☐ Some of the research procedures and/or child groups
- Complete the table below and then to go [question 7.5.a](#)

Children Group <sup>1</sup>	Describe the procedures or data/specimen collection (if any) for which assent will NOT be documented

Table footnotes

1. If the answer is the same for all children groups or all procedures, collapse the answer across the groups and/or procedures.

**a. Describe how assent will be documented.** If the children are functionally illiterate or are not fluent in English, include a description of the documentation process for them.

**b. Upload all assent materials** (talking points, videos, forms, etc.) to **Zipline**. Assent materials are not required to provide all of the standard elements of adult consent; the information should be appropriate to the age, population, and research procedures. The documents should be in Word, if possible.

**7.6 Children who reach the legal age of consent during participation in longitudinal research.**

Children who were enrolled at a young age and continue for many years: It is best practice to re-obtain assent (or to obtain it for the first time, if it was not obtained at the beginning of their participation).

Children who reach the legal age of consent: Informed consent must be obtained from the now-adult subject for (1) any ongoing interactions or interventions with the subjects, or (2) the continued analysis of specimens or data for which the subject's identify is readily identifiable to the researcher, unless the IRB waives this requirement.

a. Describe the plans (if any) to re-obtain assent from children.

b. Describe the plans (if any) to obtain consent for children who reach the legal age of consent.

- If adult consent will be obtained from them, describe what will happen regarding now-adult subjects who cannot be contacted.
- If consent will not be obtained or will not be possible: explain why.

**7.7 Other regulatory requirements.** (This is for information only; no answer or response is required.) Researchers are responsible for determining whether their research conducted in schools, with student records, or over the Internet comply with permission, consent, and inspection requirements of the following federal regulations:

- PPRA – Protection of Pupil Rights Amendment
- FERPA – Family Education Rights and Privacy Act
- COPPA – Children’s Online Privacy Protection Act

## 8 CONSENT OF ADULTS

Review the following definitions before answering the questions in this section.

<b>CONSENT</b>	is the <u>process</u> of informing potential subjects about the research and asking them whether they want to participate. It does not necessarily include the signing of a consent form.
----------------	---

<b>CONSENT DOCUMENTATION</b>	refers to how a subject’s decision to participate in the research is documented. This is typically obtained by having the subject sign a consent form.
------------------------------	--

<b>CONSENT FORM</b>	is a document signed by subjects, by which they agree to participate in the research as described in the consent form and in the consent process.
---------------------	---

<b>ELEMENTS OF CONSENT</b>	are specific information that is required to be provided to subjects.
----------------------------	---

<b>CHARACTERISTICS OF CONSENT</b>	<p>are the qualities of the consent process as a whole. These are:</p> <ul style="list-style-type: none"><li>• Consent must be legally effective.</li><li>• The process minimizes the possibility of coercion or undue influence.</li><li>• Subjects or their representatives must be given sufficient opportunity to discuss and consider participation.</li><li>• The information provided must:<ul style="list-style-type: none"><li>○ Begin with presentation of key information (for consent materials over 2,000 words)</li><li>○ Be what a reasonable person would want to have</li><li>○ Be organized and presented so as to facilitate understanding</li><li>○ Be provided in sufficient detail</li><li>○ Not ask or appear to ask subjects to waive their rights</li></ul></li></ul>
-----------------------------------	--

<b>PARENTAL PERMISSION</b>	is the parent's active permission for the child to participate in the research. Parental permission is subject to the same requirements as consent, including written documentation of permission and required elements.
<b>SHORT FORM CONSENT</b>	is an alternative way of obtaining written documentation of consent that is most commonly used with individuals who are illiterate or whose language is one for which translated consent forms are not available.
<b>WAIVER OF CONSENT</b>	means there is IRB approval for not obtaining consent or for not including some of the elements of consent in the consent process.
<b>WAIVER OF DOCUMENTATION OF CONSENT</b>	<b>NOTE:</b> If you plan to obtain identifiable information or identifiable biospecimens without consent, any waiver granted by the IRB does not override a subject's refusal to provide broad consent (for example, the Northwest Biobank). means that there is IRB approval for not obtaining written documentation of consent.

**8.1 Groups** Identify the groups to which the answers in this section apply.

- ☒ Adult subjects
- ☐ Parents who are providing permission for their children to participate in research

→ If you selected **PARENTS**, the word "consent" below should also be interpreted as applying to parental permission and "subjects" should also be interpreted as applying to the parents.

**8.2 The consent process and characteristics.** This series of questions is about whether consent will be obtained for all procedures except recruiting and screening and, if yes, how.

The issue of consent for recruiting and screening activities is addressed in [question 4.7](#). You do not need to repeat your answer to question 4.6.

**a. Are there any procedures for which consent will not be obtained?**

- ☐ No
- ☒ Yes → If yes, use the table below to identify the procedures for which consent will not be obtained. "All" is an acceptable answer for some studies.

Be sure to consider all research procedures and plans, including future contact, and sharing/banking of data and specimens for future work.

Group <sup>1</sup>	Describe the procedures or data/specimen collection (if any) for which there will be NO consent process	Reason why consent will not be obtained	Will subjects be provided with info about the research after they finish?	
			YES	NO
Participants prior to the most recent	Pulse oximetry data (heart rate, respiration) for participants who did not	Participants already were providing pulse ox as part of routine monitoring during fMRI scan at the CHN, so	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Document Date & Version

04/29/2021

Version 3.3

APPLICATION IRB Protocol

Researcher Date & Version

9/13/2024

Version 9.0

Page 40 of 64

amendment (MOD00018017)	provide explicit consent prior to MOD00018017	there's no change in risk to participants. We submitted a MOD to include pulse oximetry data because our primary outcome measure, which relies on skin conductance responses, have been challenging to interpret. Our intent with including pulse oximetry data (heart rate/respiration) is to facilitate interpretation of the skin conductance data because theoretically they tap into the same physiological arousal system. This modification was approved on 1/25/24. At that time, 47 participants were enrolled in the study and 41 completed the study. This means we would need to reach out to 41 participants by email or phone to obtain consent for using pulse ox data in our analyses. Not all participants will respond and without a waiver of consent, we may not have enough of a sample to use the data for interpreting skin conductance responses. Not getting consent from participants will not put them at harm since these data has already been collected.		
			<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>

Table footnotes

1. *If the answer is the same for all groups, collapse your answer across the groups and/or procedures.*

- b. Describe the consent process**, if consent will be obtained for any or all procedures, for any or all groups. Address groups and procedures separately if the consent processes are different.

*Be sure to include:*

- *The location/setting where consent will be obtained*
- *Who will obtain consent (refer to positions, roles, or titles, not names)*
- *How subjects will be provided sufficient opportunity to discuss the study with the research team and consider participation*

Verbal non-written consent will be obtained by the study research assistant conducting the initial phone screening interview to proceed with asking about eligibility criteria. Electronic consent will be obtained by a trained member of the study staff (e.g., PI or graduate student clinician) for the in-person study visit prior to

Document Date & Version

04/29/2021

Version 3.3

APPLICATION IRB Protocol

Researcher Date & Version

9/13/2024

Version 9.0

Page 41 of 64

initiating other study procedures. Electronic consent will be provided in the (in-person) presence of study staff to verify identity and witness signing through the UW ITHS-hosted REDCap tool.

- c. **Comprehension.** Describe the methods that will be used to ensure or test the subjects' understanding of the information during the consent process.

Only participants who are between 18-45 years old and fluent in English will participate in the study. This will limit age- and language-related barriers contributing to the understanding of the consent process. The consent form presented to each subject will be written in lay language, avoiding technical or confusing wording. Participants will be provided a copy of the consent form via email when we schedule the first visit so that they are given a chance to review it ahead of time. Study staff will also review each main point of the consent form verbally and answer any questions that may arise during the study visit.

- d. **Influence.** Does the research involve any subject groups that might find it difficult to say "no" to participation because of the setting or their relationship with someone on the study team, even if they aren't pressured to participate?

*Examples: Student participants being recruited into their teacher's research; patients being recruited into their healthcare provider's research, study team members who are participants; outpatients recruited from an outpatient surgery waiting room just prior to their surgery.*

<input type="checkbox"/>
<input checked="" type="checkbox"/>

No

Yes

→ If yes, describe what will be done to reduce any effect of the setting or relationship on the participation decision.

*Examples: a study coordinator will obtain consent instead of the subjects' physician; the researcher will not know which subjects agreed to participate; subjects will have two days to decide after hearing about the study.*

There is some pilot testing that will need to be done on the electrical stimulation equipment together with the MRI, as well as outside of the MRI in the mock scanner. This will involve testing among lab members for portions of the study protocol. Any lab members who participate in pilot testing (either administering study procedures or completing study procedures) will be provided verbal informed consent provided by another qualified member of the study staff to ensure there is no coercion and that lab members understand they are not required to participate in pilot testing.

- e. **Information provided is tailored to needs of subject population.** Describe the basis for concluding that the information that will be provided to subjects (via written or oral methods) is what a *reasonable member of the subject population(s)* would want to know. If the research consent materials contain a key information section, also describe the basis for concluding that the information presented in that section is that which is *most likely* to assist the selected subject population with making a decision. See [GUIDANCE Key Information for Consent Materials](#).

*For example: Consultation with publications about research subjects' preferences, disease-focused nonprofit groups, patient interest groups, or other researchers/study staff with experience with the specific population. It may also involve directly consulting selected members of the study population.*

Dr. Fang has been directly working with patients with social anxiety disorder since 2009 and has written several publications on developing efficacious treatments for this specific population.

f. Ongoing process. For research that involves multiple or continued interaction with subjects over time, describe the opportunities (if any) that will be given to subjects to ask questions or to change their minds about participating.

Participants will be informed during the initial phone screening interview and during the in-person consenting process that they will be able to terminate participation in the study at any point without penalty. Participants will also have the contact information of the PI and the study research assistant, if they have any questions or concerns at any time during or after participation.

In regards to timing and compensation updates, both former and current subjects who would be affected will be informed of the update. Former and current subjects who complete their participation prior to the modification approval and run at or surpass 4 ½ hours will be emailed about changes to the protocol and will be compensated appropriately. Former subjects who did not reach 4 ½ hours will not be contacted since this modification approval would not affect their compensation.

**8.3 Electronic presentation of consent information.** Will any part of the consent-related information be provided electronically for some or all of the subjects?

*This refers to the use of electronic systems and processes instead of (or in addition to) a paper consent form. For example, an emailed consent form, a passive or an interactive website, graphics, audio, video podcasts. See [GUIDANCE Electronic Informed Consent](#) for information about electronic consent requirements at UW.*

No

→ If no, skip to [question 8.4](#)

☒ **Yes** → If yes, answer questions **a** through **e**

**a.** Describe the electronic consent methodology and the information that will be provided.

*All informational materials must be made available to the IRB. Website content should be provided as a Word document. It is considered best practice to give subjects information about multi-page/multi-screen information that will help them assess how long it will take them to complete the process. For example, telling them that it will take about 15 minutes, or that it involves reading six screens or pages.*

Participants will be emailed a copy of the consent form to review ahead of time when scheduling their initial study appointment. During the initial study appointment, participants will review the consent form together with a trained member of the study staff (e.g., PI, graduate student clinician) and will be asked to sign the consent form electronically through REDCap (hosted through the ITHS). Documentation of informed consent will also be stored electronically on REDCap.

**b.** Describe how the information can be navigated (if relevant). *For example, will the subject be able to proceed forward or backward within the system, or to stop and continue at a later time?*

Participants will be guided through the electronic consent process during the initial study appointment with a trained member of the study staff and will be able to proceed forward and backward within the system, only with guidance from the study staff member.

**c.** In a standard paper-based consent process, the subjects generally have the opportunity to go through the consent form with study staff and/or to ask study staff about any question they may have after reading the consent form. Describe what will be done, if anything, to facilitate the subject's comprehension and opportunity to ask questions when consent information is presented electronically. Include a description of any provisions to help ensure privacy and confidentiality during this process.

*Examples: hyperlinks, help text, telephone calls, text messages or other type of electronic messaging, video conference, live chat with remotely located study team members.*

As described above, consent will be obtained during the initial study appointment with a trained member of the study staff. The study staff member will review aspects of the study procedure to answer questions in real time with the participant as they arise. The research assistant will also email the consent form ahead of the visit to give the participant plenty of time to review it before the appointment.

**d.** What will happen if there are individuals who wish to participate but who do not have access to the consent methodology being used, or who do not wish to use it? Are there alternative ways in which they can obtain the information, or will there be some assistance available? If this is a clinical trial, these individuals cannot be excluded from the research unless there is a compelling rationale.

*For example, consider individuals who lack familiarity with electronic systems, have poor eyesight or impaired motor skills, or who do not have easy email or internet access.*

If a participant is unable to complete the consent process electronically, we would consent that participant using paper consent forms. We will then upload a scanned copy of the signed consent form into REDCap and provide documentation of informed consent in REDCap, as usual.

- e. How will the research team ensure continued accessibility of consent materials and information during the study?

Research assistants will be readily available to address any questions or concerns the participant may have about the consent process, and throughout the entirety of the study. Participants will be encouraged to ask questions about the study whenever they arise to any member of the study staff or the study PI. A signed copy of the consent form will also be emailed to participants (or given to patients in paper format if they prefer) after the consenting process to have as a reference throughout the duration of the study.

- f. How will additional information be provided to subjects during the research, including any significant new findings (such as new risk information) If this is not an issue, explain why.

Since this study involves only one in-person visit, it is unlikely that new information during any individual subject's participation in the research will be interrupted due to the discovery of significant new findings. Should new risk information emerge as a result of unanticipated problems or serious adverse events that require unblinding in order to determine its relation to the active study drug, we will notify all enrolled participants, as well as previously enrolled participants. We will also consult with the DSMB, FDA, and IRB in this rare circumstance to ensure the safety of subjects.

**8.4 Written documentation of consent.** Which of the statements below describe whether documentation of consent will be obtained? NOTE: This question does not apply to screening and recruiting procedures which have already been addressed in [question 4.7](#).

*Documentation of consent that is obtained electronically is not considered written consent unless it is obtained by a method that allows verification of the individual's signature. In other words, saying "yes" by email is rarely considered to be written documentation of consent*

- a. Is written documentation of consent being obtained for:

- ☐ None of the research procedures → Use the table below to provide justification then go to [question 8.5](#).
- ☒ All of the research procedures → Do not complete the table; go to [question 8.4.b](#).
- ☐ Some of the research procedures → Use the table below to identify the procedures for which written documentation of consent will not be obtained from adult subjects.

Adult subject group <sup>1</sup>	Describe the procedures or data/specimen collection (if any) for which there will be NO documentation of consent	Will they be provided with a written statement describing the research (optional)?	
		YES	NO
		<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>

Document Date & Version

04/29/2021

Version 3.3

APPLICATION IRB Protocol

Researcher Date & Version

9/13/2024

Version 9.0

Page 45 of 64


#### Table footnotes

1. If the answer is the same for all adult groups or all procedures, collapse the answer across the groups and/or procedures.

**b. Electronic consent signature.** For studies in which documentation of consent will be obtained: will subjects use an electronic method to provide their consent signature?

- See the [GUIDANCE Electronic Informed Consent](#) for information about options (including REDCap e-signature and the DocuSign system) and any associated requirements.
- FDA-regulated studies must use a system that complies with the FDA's "Part 11" requirements about electronic systems and records. Note that the UW-IT supported DocuSign e-signature system does not meet this requirement.
- Having subjects check a box at the beginning of an emailed or web-based questionnaire is not considered legally effective documentation of consent.

<input type="checkbox"/>
<input checked="" type="checkbox"/>

No

Yes

→ If yes, indicate which methodology will be used.

<input checked="" type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>

UW ITHS REDCap

Other REDCap  
installation

UW DocuSign

Other

→ Please name the institutional version you will be using (e.g. Vanderbilt, Univ. of Cincinnati) in the field below and provide a completed **SUPPLEMENT Other REDCap Installation** with your submission.

→ Please describe in the field below and provide a signed [TEMPLATE Other E-signature Attestation Letter](#) with your submission.

**b.1** Is this method legally valid in the jurisdiction where the research will occur?

*NOTE: UW ITHS REDCap and UW DocuSign have been vetted for compliance with WA State and federal laws regarding electronic signatures.*

<input type="checkbox"/>
<input checked="" type="checkbox"/>

No

Yes → If yes, what is the source of information about legal validity?

**b.2** Will verification of the subject's identity be obtained if the signature is not personally witnessed by a member of the study team? Note that this is required for FDA-regulated studies.

See the [GUIDANCE Electronic Informed Consent](#) for information and examples

☒ **No** → If no, provide the rationale for why this is not required or necessary to protect subjects or the integrity of the research. Also, what would be the risks to the actual subject if somebody other than the intended signer provides the consent signature?

Subjects will only be able to provide electronic consent in REDCap in the (in-person) presence of a trained member of the study staff.

☐ **Yes** → If yes, describe how subject identity will be verified, providing a non-technical description that the reviewer will understand.

**b.3** How will the requirement be met to provide a copy of the consent information (consent form) to individuals who provide an e-signature?

*The copy can be paper or electronic and may be provided on an electronic storage device or via email. If the electronic consent information uses hyperlinks or other websites or podcasts to convey information specifically related to the research, the information in these hyperlinks should be included in the copy provided to the subjects and the website must be maintained for the duration of the entire study.*

Participants will be sent a secure email with a signed copy of the consent form.

**8.5 Non-English-speaking or -reading adult subjects.** Will the research enroll adult subjects who do not speak English or who lack fluency or literacy in English?

☒ **No**

☐ **Yes** → If yes, describe the process that will be used to ensure that the oral and written information provided to them during the consent process and throughout the study will be in a language readily understandable to them and (for written materials such as consent forms or questionnaires) at an appropriate reading/comprehension level.

**a. Interpretation.** Describe how interpretation will be provided, and when. Also, describe the qualifications of the interpreter(s) – for example, background, experience, language proficiency in English and in the other language, certification, other credentials, familiarity with the research-related vocabulary in English and the target language.

**b. Translations.** Describe how translations will be obtained for all study materials (not just consent forms). Also, describe the method for ensuring that the translations meet the UW IRB's requirement that translated documents will be linguistically accurate, at an appropriate reading level for the participant population, and culturally sensitive for the locale in which they will be used.

**8.6 Barriers to written documentation of consent.** There are many possible barriers to obtaining written documentation of consent. Consider, for example, individuals who are functionally illiterate; do not read English well; or have sensory or motor impairments that may impede the ability to read and sign a consent form.

- a. Describe the plans (if any) for obtaining written documentation of consent from potential subjects who may have difficulty with the standard documentation process (that is, reading and signing a consent form). Skip this question if written documentation of consent is not being obtained for any part of the research.

*Examples of solutions: Translated consent forms; use of the Short Form consent process; reading the form to the person before they sign it; excluding individuals who cannot read and understand the consent form.*

A trained member of the study staff will review the consent form in detail with participants before signing. We will also exclude individuals who cannot read and understand the consent form.

**8.7 Deception.** Will information be deliberately withheld, or will false information be provided, to any of the subjects?

*Note: "Blinding" subjects to their study group/condition/arm is not considered to be deception, but not telling them ahead of time that they will be subject to an intervention or about the purpose of the procedure(s) is deception.*

☐ No  
☒ Yes

→ If yes, describe what information and why.

*Example: It may be necessary to deceive subjects about the purpose of the study (describe why).*

Pilot subjects will purposefully not be informed that (1) that they are pilot subjects, and (2) they will only receive the placebo condition. Pilot subjects will still be consented with the approved consent form, which includes typical randomization policies into a control or placebo condition. Pilot subjects will be deceived because it is believed that the knowledge of this information may affect the results of the study.

- a. Will subjects be informed beforehand that they will be unaware of or misled regarding the nature or purposes of the research? (Note: this is not necessarily required.)

☒ No  
☐ Yes

- b. Will subjects be debriefed later? (Note: this is not necessarily required.)

☐ No  
☒ Yes

→ If yes, describe how and when this will occur. Upload any debriefing materials, including talking points or a script, to **Zipline**.

Participants will be debriefed at the end of the study to assess their expectancies of the drug, reactions to MRI, and determine whether follow-up for any reported adverse events is needed. See attached document describing debriefing talking points.

**8.8 Cognitively impaired adults, and other adults unable to consent.** Will such individuals be included in the research?

*Examples: individuals with Traumatic Brain Injury (TBI) or dementia; individuals who are unconscious, or who are significantly intoxicated.*

☒ No → If no, go to [question 8.9](#).

☐ **Yes** → If yes, answer the following questions.

a. Rationale. Provide the rationale for including this population.

b. Capacity for consent / decision making capacity. Describe the process that will be used to determine whether a cognitively impaired individual is capable of consent decision making with respect to the research protocol and setting.

b.1. If there will be repeated interactions with the impaired subjects over a time period when cognitive capacity could increase or diminish, also describe how (if at all) decision-making capacity will be re-assessed and (if appropriate) consent obtained during that time.

c. Permission (surrogate consent). If the research will include adults who cannot consent for themselves, describe the process for obtaining permission ("surrogate consent") from a legally authorized representative (LAR).

*For research conducted in Washington State, see the [GUIDANCE Legally Authorized Representative](#) to learn which individuals meet the state definition of "legally authorized representative".*

d. Assent. Describe whether assent will be required of all, some, or none of the subjects. If some, indicate which subjects will be required to assent and which will not (and why not). Describe any process that will be used to obtain and document assent from the subjects.

e. Dissent or resistance. Describe how a subject's objection or resistance to participation (including non-verbal) during the research will be identified, and what will occur in response.

**8.9 Research use of human fetal tissue obtained from elective abortion.** Federal and UW Policy specify some requirements for the consent process. If you are conducting this type of research, check the boxes to confirm these requirements will be followed.

☐ Informed consent for the donation of fetal tissue for research use will be obtained by someone other than the person who obtained the informed consent for abortion.

☐ Informed consent for the donation of fetal tissue for research use will be obtained after the informed consent for abortion.

☐ Participation in the research will not affect the method of abortion.

☐ No enticements, benefits, or financial incentives will be used at any level of the process to incentivize

abortion or the donation of human fetal tissue.

☐

The informed consent form for the donation of fetal tissue for use in research will be signed by both the woman and the person who obtains the informed consent.

**8.10 Consent-related materials.** Upload to **Zipline** all consent scripts/talking points, consent forms, debriefing statements, Information Statements, Short Form consent forms, parental permission forms, and any other consent-related materials that will be used. Materials that will be used by a specific site should be uploaded to that site's **Local Site Documents** page.

- *Translations must be submitted and approved before they can be used. However, we strongly encourage you to wait to provide them until the IRB has approved the English versions.*
- *Combination forms: It may be appropriate to combine parental permission with consent, if parents are subjects as well as providing permission for the participation of their children. Similarly, a consent form may be appropriately considered an assent form for older children.*
- *For materials that cannot be uploaded: upload screenshots or written descriptions that are sufficient to enable the IRB to understand the types of data that will be collected and the nature of the experience for the participant. URLs (website addresses) may also be provided, or written descriptions of websites. Examples of materials that usually cannot be uploaded: mobile apps; computer-administered test; licensed and restricted standardized tests.*

## 9 PRIVACY AND CONFIDENTIALITY

**9.1 Privacy protections.** Describe the steps that will be taken, if any, to address possible privacy concerns of subjects and potential subjects.

*Privacy refers to the sense of being in control of access that others have to ourselves. This can be an issue with respect to recruiting, consenting, sensitivity of the data being collected, and the method of data collection.*

*Examples:*

- *Many subjects will feel a violation of privacy if they receive a letter asking them to participate in a study because they have \_\_\_\_ medical condition, when their name, contact information, and medical condition were drawn from medical records without their consent. Example: the IRB expects that "cold call" recruitment letters will inform the subject about how their information was obtained.*
- *Recruiting subjects immediately prior to a sensitive or invasive procedure (e.g., in an outpatient surgery waiting room) will feel like an invasion of privacy to some individuals.*
- *Asking subjects about sensitive topics (e.g. details about sexual behavior) may feel like an invasion of privacy to some individuals.*

Upon initial contact with our study staff, participants will be asked what their preferred method of communication is to protect their privacy. A trained member of the study staff will also discuss with potential participants about possible risks to privacy during the consenting process. Participants will also be informed that certain study procedures (clinical interviews, self-report questionnaires, social learning task, fMRI scan) may involve discomfort and that they can discontinue participation at any point.

**9.2 Identification of individuals in publications and presentations.** Will potentially identifiable information about subjects be used in publications and presentations, or is it possible that individual identities could be inferred from what is planned to be published or presented?

☒

No

☐ Yes → If yes, will subject consent be obtained for this use?

☐ Yes

☐ No

→ If no, describe the steps that will be taken to protect subjects (or small groups of subjects) from being identifiable.

**9.3 State mandatory reporting.** Each state has reporting laws that require some types of individuals to report some kinds of abuse, and medical conditions that are under public health surveillance. These include:

- Child abuse
- Abuse, abandonment, neglect, or financial exploitation of a vulnerable adult
- Sexual assault
- Serious physical assault
- Medical conditions subject to mandatory reporting (notification) for public health surveillance

Are you or a member of the research team likely to learn of any of the above events or circumstances while conducting the research **AND** feel obligated to report it to state authorities?

☐ No

☒ Yes → If yes, the UW IRB expects subjects to be informed of this possibility in the consent form or during the consent process, unless you provide a rationale for not doing so:

**9.4 Retention of identifiers and data.** Check the box below to indicate assurance that any identifiers (or links between identifiers and data/specimens) and data that are part of the research records will not be destroyed until after the end of the applicable records retention requirements (e.g. Washington State; funding agency or sponsor; Food and Drug Administration). If it is important to say something about destruction of identifiers (or links to identifiers) in the consent form, state something like “the link between your identifier and the research data will be destroyed after the records retention period required by state and/or federal law.”

*This question can be left blank for conversion applications (existing paper applications that are being “converted” into a Zipline application.)*

*See the “Research Data” sections of the following website for UW Records management for the Washington State research records retention schedules that apply in general to the UW (not involving UW Medicine data):*

<http://f2.washington.edu/fm/recmgmt/gs/research?title=R>

*See the “Research Records and Data” information in Section 8 of this document for the retention schedules for UW Medicine Records: <https://www.uwmedicine.org/recordsmanagementuwm-records-retention-schedule.pdf>*

☒ Confirm

**9.5 Certificates of Confidentiality.** Will a federal Certificate of Confidentiality be obtained for the research data?  
*NOTE: Answer “No” if the study is funded by NIH or the CDC, because all NIH-funded and CDC-funded studies automatically have a Certificate.*

☐ No

☒ Yes

**9.6 Data and specimen security protections.** Identify the data classifications and the security protections that will be provided for all sites where data will be collected, transmitted, or stored, referring to the [GUIDANCE Data and Security Protections](#) for the minimum requirements for each data classification level. ***It is not possible to answer this question without reading this document. Data security protections should not conflict with records retention requirements.***

- a. Which level of protections will be applied to the data and specimens? If more than one level will be used, describe which level will apply to which data and which specimens and at which sites.

Level 4 protections will be applied to the data in this study [in accordance with HSD's current guidance](#).

- b. Use this space to provide additional information, details, or to describe protections that do not fit into one of the levels. If there are any protections within the level listed in 9.6.a which will *not* be followed, list those here, including identifying the sites where this exception will apply.

A certificate of confidentiality will be obtained to mitigate risk of data breaches with regard to urine drug screening tests that will be performed in the study.

## 10 RISK / BENEFIT ASSESSMENT

**10.1 Anticipated risks.** Describe the reasonably foreseeable risks of harm, discomforts, and hazards to the subjects and others of the research procedures. For each harm, discomfort, or hazard:

- Describe the magnitude, probability, duration, and/or reversibility of the harm, discomfort, or hazard, AND
- Describe how the risks will be reduced or managed. Do not describe data security protections here, these are already described in Question 9.6.
- *Consider possible physical, psychological, social, legal, and economic harms, including possible negative effects on financial standing, employability, insurability, educational advancement or reputation. For example, a breach of confidentiality might have these effects.*
- *Examples of "others": embryo, fetus, or nursing child; family members; a specific group.*
- *Ensure applicable risk information from any Investigator Brochures, Drug Package Inserts, and/or Device Manuals is included in your description.*
- *Do not include the risks of non-research procedures that are already being performed.*
- *If the study design specifies that subjects will be assigned to a specific condition or intervention, then the condition or intervention is a research procedure - even if it is a standard of care.*
- *Examples of mitigation strategies: inclusion/exclusion criteria; applying appropriate data security measures to prevent unauthorized access to individually identifiable data; coding data; taking blood samples to monitor something that indicates drug toxicity.*
- *As with all questions on this application, you may refer to uploaded documents.*

### Potential Risks to Participation

Risks of oxytocin and placebo nasal sprays:

- Allergic reaction – extremely rare, moderate to severe
- The Investigator Brochure from Tonix Pharmaceuticals references safety data from 23 published clinical trials (n = 531) that have examined daily repeated administration of intranasal oxytocin. Intranasal oxytocin was shown to be generally safe and well-tolerated in healthy and patient populations across the entire lifespan (infants, children, adolescents, adults, and the elderly) (p.36, Table 11). Common AEs (nasal discomfort, irritability, tiredness, diarrhea, skin irritation, headache or migraine) were mild and transient, and rates were not distinguishable from placebo (Cai et al., 2018). From published studies, there were 6 cases of severe AEs (seizure, hyperactivity and aggression, gynecomastia) following IN OT, however these were not deemed to be causally linked to IN OT. The

antidiuretic effect associated with high levels of oxytocin when coupled with excessive fluid intake can cause reduced sodium levels and water intoxication (MacDonald et al., 2011).

- A study examining side effects of intranasal oxytocin in studies conducted between 1990 and 2010 identified 38 controlled studies involving intranasal delivery of oxytocin (MacDonald et al., 2011). A total of 1,529 participants received intranasal oxytocin or placebo, and nine studies included participants (N=182) who had a developmental, medical, or mental health disorder. The dosage of oxytocin was typically a single dose ranging from 20 international units (IU) to 40 IU. Out of the 1,529 participants who received intranasal oxytocin or placebo, 279 (18%) reported mild side-effects (MacDonald et al., 2011). The most common side-effect was a feeling of calmness, but this did not differ between those who received oxytocin or placebo. A recent review of studies using intranasal oxytocin supported the short-term use of oxytocin, demonstrating that oxytocin produced minimal side-effects, no detectable differences in side-effects between oxytocin or placebo recipients, no subjective changes in recipients, and is equally safe to use with vulnerable populations as with healthy adults (MacDonald et al., 2011).
- Side effects reported in mothers during labor who are treated with IV Syntocinon® or Pitocin®, which are commercially available brands of oxytocin, include headaches, nausea, irregular heartbeat, bleeding or lack of blood clotting, nausea, and vomiting – Not expected as we will be excluding pregnant women
- In this study the possible AE's that might arise include lightheadedness/vertigo, tiredness/drowsiness/sleepiness, difficulty sitting still, dry throat/mouth, nasal/throat irritation/discomfort, runny nose, abdominal/stomach pain, feeling anxious/worried/uncomfortable, irritability, diarrhea, skin irritation, or headaches/migraines.

#### Risks of MRI scan and clinical/self-report assessments:

- Feeling of claustrophobia, anxiety or panic during MRI scan
- Noise discomfort during MRI scan
- Incidental findings during MRI scan
- Discomfort or anxiety discussing personal material during clinical/self-report assessments
- Prolonged use of infrared light from the EyeLink1000 can cause discomfort due to slight drying to the eyes, especially for those who wear contact lenses.

#### Risks of electrical stimulation during social learning task:

- Redness at the point of stimulation
- Physical discomfort (e.g., skin rash and/or itching due to electrode gel used for conductance)
- Psychological discomfort (e.g., nervousness)
- Minor injuries, such as burns, or in very rare cases with higher powered stimulators major injuries, such as nerve, tissue, or organ damage, if equipment is used improperly resulting in stimulation with high voltages

#### Risk of disclosure:

- We may be required by law to share information with third parties (including public safety or law enforcement authorities) if we learn information that indicates an intent to seriously harm others or themselves, and may need to take other precautions to protect against such harm. Theft or court order could also be unforeseen circumstances that result in disclosure of this information outside of the context of this research study.
- Breach of confidentiality represents a potential risk. However, we will take great precautions to ensure that this potential risk is minimized.
- There is a legal risk of harm of the urine drug test (e.g., if there were a data breach and records were accessed).

## **Risk Reduction and Management Procedures**

### **Management of risks of oxytocin and placebo nasal sprays:**

- Participants will be informed that if they wish to stop breathing the nasal sprays, they can stop at any time and tell the study nurse (who will be with them when they inhale the nasal spray).
- A study nurse will take subjects' vitals before they inhale the nasal spray to ensure that they are physically fit to receive the drug. The nurse will be with participants while they inhale the nasal spray, and for 15 minutes afterwards. After subjects inhale the nasal spray, the study nurse will take their vital signs again to check for signs of a reaction. Immediately after drug administration, nurses will review the Adverse Events Form and research staff will assess acute suicidal ideation using a brief standardized risk assessment.
- The present study will use a single administration of 24 IU of intranasal oxytocin (or placebo), which is the most commonly used dose in previous experimental studies of intranasal oxytocin (Quintana et al., 2020).
- A urine drug screening test will be performed prior to oxytocin administration. A positive result will result in withdrawal from the study.

### **Management of risks of MRI scan and clinical/self-report assessments:**

- Participants will be given a mock scan prior to the actual MRI scan.
- Screening procedures will exclude any individuals who are not clinically suitable for the study protocol, for example, with clinically significant suicidality or claustrophobia. Participants will also be thoroughly screened both prior to the study and at the beginning of each in-person visit to make sure that they have no metal implants or any other contraindications to MRI. Women will complete a urine pregnancy test prior to each scan. A positive test will result in withdrawal from the study.
- While in the scanner, participants will be able to converse with study staff via a microphone and speaker system between scans.
- Participants will be provided a squeeze ball during MRI scanning they can use to request stopping the scan at any time
- Participants will be able to wear normal street clothes, so long as they are MRI safe (e.g. no metal antimicrobial materials or ferrous metal on the clothing), without changing into medical scrubs before undergoing MRI to reduce discomfort.
- Participants will be given earplugs while in the scanner to minimize discomfort to the noise in the scanner.
- Participants will be carefully monitored during all study procedures and by nursing staff after receiving the nasal spray. Adverse events will be assessed, recorded, and study staff will follow-up with participants to ensure adverse events are resolved by the end of the study visit.
- Subjects are likely to experience the 100 ms DC-pulse electric stimulation applied to their right wrist as **uncomfortable**. The shock level will be adjusted by each subject prior to the start of the experiment to be perceived as uncomfortable but not painful. Subjects will decide for themselves the level of current we use during testing sessions.
- Due to the risk of discomfort from dryness to the eyes at close distances using the EyeLink1000, participants will not undergo eye tracking for extended periods of time at distances less than 6 inches from the eye.
- Participants will be informed they can stop participation in the study at any time.
- Study staff will make every attempt to help participants feel comfortable when discussing sensitive material.

- Participants will be encouraged to contact investigators after the study if new adverse events were to emerge.

Management of risks of electrical stimulation: (see Lab-wide SOP for safe use of electrical stimulation in human subjects for full details)

- Stimulation systems have been set up with extensive consultation with BIOPAC Systems, Inc technical support team to maintain safety in both MR-compatible and non-MR-compatible systems for use inside the MRI and in the mock scanner.
- We are using BIOPAC's recommended stimulation setup for use with MRI, which includes use of patch panel filters and a current feedback monitoring system to monitor actual current delivered to the participant.
- We will only use MR-compatible leads and electrodes for use inside the scanner, and non-MR-compatible leads and electrodes for use outside the scanner.
- We will monitor levels of actual current delivered to the participant during the study.
- We will conduct testing prior to study enrollment to confirm the maximum current output to be delivered to participants (e.g., 24mA)- see SOP for further details.
- We will start the stimulation process with the control set to a relatively low level (e.g., 4 mA), which is imperceptible to most participants.
- We will individually calibrate the participant's level of stimulation intensity based on perceived shocks that are uncomfortable, but not painful.
- We will inform participants at the beginning and throughout the experiment about their right to stop the experiment at any point without penalty.
- We will train all study staff in proper device use, electrode placement, and software use, and receive shocks themselves to provide awareness of what the shocks should feel like and how to calibrate shock intensity from being unduly painful.

Management of risks of disclosure:

- Study data will be reviewed only by pre-designated study personnel.
- All personnel will be thoroughly trained in research confidentiality procedures and will be educated about the importance of strictly protecting participants' rights to confidentiality.
- To reduce the risk of a data breach in which urine drug test results could be accessed, we will be letting participants know ahead of time of the sensitive data that will be collected in the study and obtaining a Certificate of Confidentiality.

**10.2 Reproductive risks.** Are there any risks of the study procedures to men and women (who are subjects, or partner of subjects) related to pregnancy, fertility, lactation or effects on a fetus or neonate?

*Examples: direct teratogenic effects; possible germline effects; effects on fertility; effects on a woman's ability to continue a pregnancy; effects on future pregnancies.*

<input type="checkbox"/>
<input checked="" type="checkbox"/>

No  
Yes

→ If no go to [question 10.3](#)

→ If yes, answer the following questions:

**a. Risks.** Describe the magnitude, probability, duration and/or reversibility of the risks.

There is a risk of oxytocin related to current pregnancy as oxytocin can induce labor in pregnant women. There are also unknown risks of MRI scanning to an unborn fetus.

**b. Steps to minimize risk.** Describe the specific steps that will be taken to minimize the magnitude, probability, or duration of these risks.

*Examples: inform the subjects about the risks and how to minimize them; require a pregnancy test before and during the study; require subjects to use contraception; advise subjects about banking of sperm and ova.*

*If the use of contraception will be required: describe the allowable methods and the time period when contraception must be used.*

We will inform subjects about these risks in oxytocin administration, MRI scanning, and pregnancy during the consent process. We will pre-screen for pregnancy or breastfeeding via self-report in the phone screen and eligibility form. The CHN will also screen for pregnancy via self-report, as pregnant individuals will not be eligible to be scanned in the MRI at the CHN. If a participant indicates via self-report that they are pregnant or breastfeeding they will also be withdrawn from the study. We will also obtain a urine pregnancy test result from female subjects prior to oxytocin administration at the study visit, to ensure that none are pregnant. A positive pregnancy test will result in withdrawal from the study.

**c. Pregnancy.** Describe what will be done if a subject (or a subject's partner) becomes pregnant

*For example; will subjects be required to immediately notify study staff, so that the study procedures can be discontinued or modified, or for a discussion of risks, and/or referrals or counseling?*

Subjects who become pregnant will be required to immediately notify study staff if they are in the process of scheduling study visits so that study visits can be canceled.

**10.3 MRI risk management.** A rare but serious adverse reaction called nephrogenic systemic fibrosis (NSF) has been observed in individuals with kidney disease who received gadolinium-based contrast agents (GBCAs) for the scans. Also, a few healthy individuals have a severe allergic reaction to GBCAs.

**a. Use of gadolinium.** Will any of the MRI scans involve the use of a gadolinium-based contrast agent (GBCA?)

<input checked="" type="checkbox"/>	No
<input type="checkbox"/>	Yes

→ If yes, which agents will be used? *Check all that apply.*

	Brand Name	Generic Name	Chemical Structure
<input type="checkbox"/>	Dotarem	Gadoterate meglumine	Macrocylic
<input type="checkbox"/>	Eovist / Primovist	Gadoxetate disodium	Linear
<input type="checkbox"/>	Gadavist	Gadobutro	Macrocylic
<input type="checkbox"/>	Magnevist	Gadpentetate dimeglumine	Linear
<input type="checkbox"/>	MultiHance	Gadobenate dimeglumine	Linear
<input type="checkbox"/>	Omniscan	Gadodiamide	Linear
<input type="checkbox"/>	OptiMARK	Gadoversetamide	Linear
<input type="checkbox"/>	ProHance	Gadoteridol	Macrocylic
<input type="checkbox"/>	Other, provide name:		

- 1.) The FDA has concluded that gadolinium is retained in the body and brain for a significantly longer time than previously recognized, especially for linear GBCAs. The health-related risks of this longer retention are not yet clearly established. However, the UW IRB expects researchers to provide a compelling justification for using a linear GBCA instead of a macrocyclic GBCA, to manage the risks associated with GBCAs.

Describe why it is important to use a GBCA with the MRI scan(s). Describe the dose that will be used and (if it is more than the standard clinical dose recommended by the manufacturer) why it is necessary to use a higher dose. If a linear GBCA will be used, explain why a macrocyclic GBCA cannot be used.

- 2.) Information for subjects. Confirm by checking this box that subjects will be provided with the FDA-approved Patient Medication Guide for the GBCA being used in the research or that the same information will be inserted into the consent form.

☒ Confirmed

- b. Who will (1) calculate the dose of GBCA; (2) prepare it for injection; (3) insert and remove the IV catheter; (4) administer the GBCA; and (5) monitor for any adverse effects of the GBCA? Also, what are the qualifications and training of these individual(s)?

- c. Describe how the renal function of subjects will be assessed prior to MRI scans and how that information will be used to exclude subjects at risk for NSF.

- d. Describe the protocol for handling a severe allergic reaction to the GBCA or any other medical event/emergency during the MRI scan, including who will be responsible for which actions.

**10.4 Unforeseeable risks.** Are there any research procedures that may have risks that are currently unforeseeable?

*Example: using a drug that hasn't been used before in this subject population.*

☒ No  
☐ Yes → If yes, identify the procedures.

**10.5 Subjects who will be under regional or general anesthesiology.** Will any research procedures occur while patients are under general or regional anesthesia, or during the 3 hours preceding general or regional anesthesia (supplied for non-research reasons)?

☒ No

☐ **Yes** → If yes, check all the boxes that apply.

- ☐ Administration of any drug for research purposes
- ☐ Inserting an intra-venous (central or peripheral) or intra-arterial line for research purposes
- ☐ Obtaining samples of blood, urine, bone marrow or cerebrospinal fluid for research purposes
- ☐ Obtaining a research sample from tissue or organs that would not otherwise be removed during surgery
- ☐ Administration of a radio-isotope for research purposes\*\*
- ☐ Implantation of an experimental device
- ☐ Other manipulations or procedures performed solely for research purposes (e.g., experimental liver dialysis, experimental brain stimulation)

If any of the boxes are checked:

Provide the name and institutional affiliation of a physician anesthesiologist who is a member of the research team or who will serve as a safety consultant about the interactions between the research procedures and the general or regional anesthesia of the subject-patients. If the procedures will be performed at a UW Medicine facility or affiliate, the anesthesiologist must be a UW faculty member, and the Vice Chair of Clinical Research in the UW Department of Anesthesiology and Pain Medicine must be consulted in advance for feasibility, safety and billing.

*\*\* If the box about radio-isotopes is checked: the study team is responsible for informing in advance all appropriate clinical personnel (e.g., nurses, technicians, anesthesiologists, surgeons) about the administration and use of the radio-isotope, to ensure that any personal safety issues (e.g., pregnancy) can be appropriately addressed. This is a condition of IRB approval.*

**10.6 Data and Safety Monitoring.** A Data and Safety Monitoring Plan (DSMP) is required for clinical trials (as defined by NIH). If required for this research, or if there is a DSMP for the research regardless of whether it is required, upload the DSMP to **Zipline**. If it is embedded in another document being uploading (for example, a Study Protocol) use the text box below to name the document that has the DSMP. Alternatively, provide a description of the DSMP in the text box below.

For information about the Data and Safety Monitoring Board and Data and Safety Monitoring Plan, please refer to the DSMP attachment in the Local Site Documents.

**10.7 Un-blinding.** If this is a double-blinded or single-blinded study in which the participant and/or relevant study team members do not know the group to which the participant is assigned: describe the circumstances under which un-blinding would be necessary, and to whom the un-blinded information would be provided.

Participants will be unblinded to the drug condition they were assigned to if they experience a serious adverse reaction to the drug that does not resolve within two hours of receiving the study drug. The PI has conducted two investigations of intranasal oxytocin in psychiatric populations and has not observed any serious or unanticipated adverse events to oxytocin.

**10.8 Withdrawal of participants.** If applicable, describe the anticipated circumstances under which participants will be withdrawn from the research without their consent. Also, describe any procedures for orderly withdrawal of a participant, regardless of the reason, including whether it will involve partial withdrawal from procedures and any intervention but continued data collection or long-term follow-up.

Participants who display active suicidal ideation at any point during the study will be withdrawn from the research to provide clinical follow-up for their symptoms.

**10.9 Anticipated direct benefits to participants.** If there are any direct research-related benefits that some or all individual participants are likely to experience from taking part in the research, describe them below:

*Do not include benefits to society or others, and do not include subject payment (if any). Examples: medical benefits such as laboratory tests (if subjects receive the results); psychological resources made available to participants; training or education that is provided.*

Participants will not benefit from taking part in this research study. However, they may contribute scientific knowledge that may benefit the study of SAD and development of novel treatments for SAD in the future.

**10.10 Return of individual research results.**

*In this section, provide your plans for the return of individual results. An “individual research result” is any information collected, generated or discovered in the course of a research study that is linked to the identity of a research participant. These may be results from screening procedures, results that are actively sought for purposes of the study, results that are discovered unintentionally, or after analysis of the collected data and/or results has been completed.*

See the [GUIDANCE Return of Individual Results](#) for information about results that should and should not be returned, validity of results, the Clinical Laboratory Improvement Amendment (CLIA), consent requirements and communicating results.

**a. Is it anticipated that the research will produce any individual research results that are clinically actionable?**

*“Clinically actionable” means that there are established therapeutic or preventive interventions or other available actions that have the potential to change the clinical course of the disease/condition, or lead to an improved health outcome.*

*In general, every effort should be made to offer results that are clinically actionable, valid and pose life-threatening or severe health consequences if not treated or addressed quickly. Other clinically actionable results should be offered if this can be accomplished without compromising the research.*

☐

No

☒

Yes

→ If yes, answer the following questions (a.1-a.3).

**a.1.** Describe the clinically actionable results that are anticipated and explain which results, if any, could be urgent (i.e. because they pose life-threatening or severe health consequences if not treated or addressed quickly).

*Examples of urgent results include very high calcium levels, highly elevated liver function test results, positive results for reportable STDs.*

Clinical participants may receive results from the diagnostic evaluation regarding issues that require clinical attention, although these results are unlikely to be urgent unless they reflect active suicidal ideation. The diagnostic evaluation that is conducted by a trained member of the study staff during the study visit includes a detailed suicidality module (Module B of the MINI 7.0.2) that will be used to assess risk, which overlaps with the “Suicide Risk Assessment” document, which will be used by research assistants during the phone screen and again by research staff at the TRU after drug

administration. In any cases of active suicidality, a plan will be made to ensure safety based on the assessment, which is further described in the “Suicide Risk Assessment” document. For example, a licensed clinician (such as the PI) may contact the participant’s treating provider to inform them of the reported suicidal ideation.

**a.2.** Explain which of these results will be offered to subjects.

Verbal results from the diagnostic evaluation will be provided to research participants enrolling in the clinical group. Additionally, results from the urine drug screening and pregnancy tests will be provided to participants.

**a.3.** Explain which results will not be offered to subjects and provide the rationale for not offering these results.

*Reasons not to offer the results might include:*

- *There are serious questions regarding validity or reliability*
- *Returning the results has the potential to cause bias*
- *There are insufficient resources to communicate the results effectively and appropriately*
- *Knowledge of the result could cause psychosocial harm to subjects*

Consistent with the incidental findings policy at the CHN, any unexpected brain abnormality will be reviewed by the Medical Director, who will recommend a course of action for managing the incidental finding. The possible outcomes include: (1) the incidental finding is non-significant so no action is needed to disclose it to the study participant, (2) the incidental finding is non-significant but the subject should be made aware that an incidental finding was made, (3) the incidental finding is significant and the subject needs to be informed.

**b.** Is there a plan for offering subjects any results that are not clinically actionable?

*Examples: non-actionable genetic results, clinical tests in the normal range, experimental and/or uncertain results.*

☐ No  
☒ Yes

→ If yes, explain which results will be offered to subjects and provide the rationale for offering these results.

As described above, one of the outcomes of an MRI-related incidental finding is that the Medical Director may determine the incidental finding to be non-significant but that the subject should still be made aware of the finding. The subject will be informed that the Medical Director will be available to answer any questions and can consult with their medical care team.

**c.** Describe the validity and reliability of any results that will be offered to subjects.

*The IRB will consider evidence of validity such as studies demonstrating diagnostic, prognostic, or predictive value, use of confirmatory testing, and quality management systems.*

The MINI diagnostic interview has been shown to have strong psychometric properties (validity and reliability) and has been cited in over 17,000 publications. Clinical data from this interview are likely to have strong validity and reliability (Sheehan et al., 1998).

MRI-related incidental findings will be reviewed by the Medical Director of CHN who has neuroradiology expertise and who will advise the PI of his/her assessment of the incidental finding.

**d.** Describe the process for communicating results to subjects and facilitating understanding of the results. In the description, include who will approach the participant with regard to the offer of results, who will communicate the result (if different), the circumstances, timing, and communication methods that will be used.

The trained study staff member who has conducted the diagnostic evaluation will communicate results to participants directly after completing the interview and provide an opportunity for participants to ask questions in order to facilitate understanding of the results.

MRI-related incidental findings that need to be disclosed to the participant will be communicated by the PI, participants will be told that the Medical Director of CHN is available to answer any questions, and/or to consult with their medical team.

- e. Describe any plans to share results with family members (e.g. in the event a subject becomes incapacitated or deceased).

N/A

- f. Check the box to indicate that any plans for return of individual research results have been described in the consent document. If there are no plans to provide results to participants, this should be stated in the consent form.

See the [GUIDANCE Return of Individual Results](#) for information about consent requirements.

☒ Confirmed

**10.11 Commercial products or patents.** Is it possible that a commercial product or patent could result from this study?

☒ No  
☐ Yes

→ If yes, describe whether subjects might receive any remuneration/compensation and, if yes, how the amount will be determined.

## 11 ECONOMIC BURDEN TO PARTICIPANTS

**11.1 Financial responsibility for research-related injuries.** Answer this question only if the lead researcher is not a UW student, staff member, or faculty member whose primary paid appointment is at the UW.

For each institution involved in conducting the research: Describe who will be financially responsible for research-related injuries experienced by subjects, and any limitations. Describe the process (if any) by which participants may obtain treatment/compensation.

**11.2 Costs to subjects.** Describe any research-related costs for which subjects and/or their health insurance may be responsible (examples might include: CT scan required for research eligibility screening; co-pays; surgical costs when a subject is randomized to a specific procedure; cost of a device; travel and parking expenses that will not be reimbursed).

Participants will be responsible for travel expenses for study visits, but will not be responsible for parking expenses. They will incur no other costs to participation.

## 12 RESOURCES

**12.1 Faculty Advisor.** (For researchers who are students, residents, fellows, or post-docs.) Provide the following information about the faculty advisor.

- Advisor's name
- Your relationship with your advisor (for example: graduate advisor; course instructor)
- Your plans for communication/consultation with your advisor about progress, problems, and changes.

N/A

**12.2 UW Principal Investigator Qualifications.** Upload a current or recent Curriculum Vitae (CV), Biosketch (as provided to federal funding agencies), or similar document to the Local Site Documents page in Zipline. The purpose of this is to address the PI's qualifications to conduct the proposed research (education, experience, training, certifications, etc.).

For help with creating a CV, see [http://adai.uw.edu/grants/nsf\\_biosketch\\_template.pdf](http://adai.uw.edu/grants/nsf_biosketch_template.pdf) and <https://education.uwmedicine.org/student-affairs/career-advising/year-4/residency-applications/curriculum-vitae/>

☒ **The CV will be uploaded.**

**12.3 UW Study team qualifications.** Describe the qualifications and/or training for each UW study team member to fulfill their role on the study and perform study procedures. (You may be asked about non-UW study team members during the review; they should not be described here.) You may list these individuals by name, however if you list an individual by name, you will need to modify this application if that individual is replaced. Alternatively, you can describe study roles and the qualifications and training the PI or study leadership will require for any individual who might fill that role. The IRB will use this information to assess whether risks to subjects are minimized because study activities are being conducted by properly qualified and trained individuals.

**Describe: The role (or name of person), the study activities they will perform, and the qualifications or training that are relevant to performing those study activities.**

**Examples:**

Research Study Coordinator: Obtain consent, administer surveys, blood draw. Will have previous experience coordinating clinical research and be a certified phlebotomist in WA.

Undergraduate Research Assistant: Obtain consent, perform all study procedures. Will have had coursework in research methods, complete an orientation to human subjects protections given by the department, and will receive training from the PI or the graduate student project lead on obtaining consent and debriefing subjects.

Acupuncturist: Perform acupuncture procedures and administer surveys. Must be licensed with WA State DoH and complete training in administering research surveys given by the project director, an experienced survey researcher.

Co-Investigator: Supervise MRI and CT scan procedures and data interpretation, obtain consent. MD, specialty in interventional radiology and body imaging. 5-years clinical research experience.

Principal Investigator: Obtain informed consent, conduct diagnostic assessment to confirm study eligibility, train all staff and oversee all study procedures

Graduate Student Clinicians: Obtain informed consent, conduct diagnostic assessment to confirm study eligibility, assist in recruitment including phone screen interviews. Graduate student clinicians have

completed coursework on clinical assessment, ethics, as well as CITI human subjects training. They have also received training in providing consent, which includes training in describing the risks and human subjects protections. They have also completed comprehensive lab reliability training requirements to be deemed certified to conduct MINI diagnostic assessments. These include a combination of live observed sessions with the PI, achieving reliability on recorded sessions, and being observed live by the PI.

Study Physician: Provide medical oversight of participants, order nasal spray prescriptions, oversee adverse events reporting

Research Assistants: Assist in recruitment, data collection (including conducting MRI scanning), and study debriefing

Study Nurses (Translational Research Unit): Assist in taking and assessing vitals, drug administration, monitoring of adverse events after drug administration

Investigational Drug Service pharmacist: Dispense nasal sprays, provide drug accountability/storage/reconciliation, and maintain study blind for randomization

**12.4 Study team training and communication.** Describe how it will be ensured that each study team member is adequately trained and informed about the research procedures and requirements (including any changes) as well as their research-related duties and functions.

☐ **There is no study team.**

The study team will undergo intensive training prior to the start of study enrollment. This will include structured training in phone screening procedures, working with sensitive clinical data, data collection procedures involving multimodal assessments (clinical/self-report/fMRI/SCR data), and protection of patient privacy and confidentiality. Study staff will also be required to complete basic human subjects training through the CITI training program.

## 13 OTHER APPROVALS, PERMISSIONS, and REGULATORY ISSUES

**13.1 Approvals and permissions.** Identify any other approvals or permissions that will be obtained. For example: from a school, external site/organization, funding agency, employee union, UW Medicine clinical unit.

*Do not attach the approvals and permissions unless requested by the IRB.*

FDA Investigational New Drug application was approved on 01/09/2023 (see attached letter). External funding for this study was awarded by the Brain and Behavior Research Foundation (formerly NARSAD) and the Royalty Research Fund.

**13.2 Financial Conflict of Interest.** Does any UW member of the team have ownership or other Significant Financial Interest (SFI) with this research as defined by [UW policy GIM 10](#)?

☒ **No**

☐ **Yes** → If yes, has the Office of Research made a determination regarding this SFI as it pertains to the proposed research?

☐ **No** → If no, contact the Office of Research (206.616.0804, [research@uw.edu](mailto:research@uw.edu)) for guidance on how to obtain the determination

☐ **Yes** → If yes, upload the Conflict Management Plan for every UW team member who has a FCOI with respect to the research, to **Zipline**. If it is not yet available, use the text box to describe whether the Significant Financial Interest has been disclosed

---

already to the UW Office of Research and include the FIDS Disclosure ID if available.