COVER PAGE

NCT number: 03302416

Official Title: In Vivo Imaging of Corticotropin-releasing Factor - Nociceptin Receptor Interactions

Document date: 11/13/2018

University of Pittsburgh **OSIRIS**

Section: Triage

[reviewer notes¬]

Provide a short title for this study (200 characters or less)**:**

CRF – nociceptin receptor interactions

T1.0

Select the type of application:
New Research Study

T2.0

Is the proposed research study limited to the inclusion of deceased individuals?
* No

T2.1

Are any research activities being conducted at the VA Pittsburgh Healthcare System or with VA funds?

* No

[reviewer notes¬]

T3.0 **What is the anticipated risk to the research participants?**

Greater Than Minimal Risk

Section: Cover Sheet

[reviewer notes¬]

CS1.0 What is the reason for this submission?

New Research Protocol Submission

CS1.1

Has this research study been approved previously by the University of Pittsburgh IRB?

* No

CS1.1.1

Has this research study (or a substantially similar research study) been previously disapproved by the University of Pittsburgh IRB or, to your knowledge, by any other IRB?

* No

[reviewer notes¬]

CS2.0

Title of Research Study:

In vivo imaging of corticotropin-releasing factor – nociceptin receptor interactions

CS2.0.1

Requested approval letter wording:

CS2.1 Research Protocol Abstract:

Basic investigations postulate that an imbalance between neurotransmitters regulating the stress and anti-stress systems underlie negative reinforcement and relapse in addiction. Nociceptin, which binds to the nociceptin/orphanin FQ peptide (NOP) receptor, is one such neuropeptide transmitter that exerts its anti-stress effects by counteracting the functional effects of corticotropin-releasing factor (CRF), the primary stress-mediating neuropeptide transmitter in the brain. Basic investigations suggest that CRF and nociceptin facilitate and inhibit anxiety-like behaviors, respectively. Convergent with this is data from animal models of alcoholism that support increased CRF and decreased nociceptin levels in the extended amygdala as the reason for anxiety-like behaviors that underlie relapse in addiction. This postulation is further supported by the ability of CRF1 receptor antagonists and NOP receptor agonists to blunt the reinforcing and motivational effects of alcohol on a range of addictive behaviors. Thus, it is of considerable interest to develop a methodology to examine CRF-NOP interactions in human addicts. Here, we will evaluate healthy humans with [C-11]NOP-1A and PET to determine if hydrocortisone-induced increases in amygdala CRF leads to altered NOP receptor binding. This experiment will for the first time document an in vivo interaction between CRF and NOP, and set the stage for evaluating if this interaction is abnormal in addiction in future investigations.

CS2.2

Select the category that best describes your research:
Biomedical research

[reviewer notes¬]

CS3.0 **Name of the Principal Investigator:**

Rajesh Narendran

Note: Adjunct faculty of the University, including lecturers and instructors, are not permitted to serve as a PI or Faculty Mentor but may serve as co-investigators. Refer to Chapter 4 on the HRPO website for more information.

CS3.1 **Affiliation of Principal Investigator:**

UPitt faculty member

If you chose any of the **Pitt options**, please indicate the specific campus:
Main Campus - Pittsburgh

If you chose the UPitt faculty member option, provide the PI's **University Faculty Title**:
Associate Professor

CS3.2

Address of Principal Investigator:

UPMC Presbyterian, B938
200 Lothrop Street
Pittsburgh, PA 15213

CS3.3 **Recorded Primary Affiliation of the Principal Investigator:**

U of Pgh | School of Medicine | Psychiatry

CS3.4 **Identify the School, Department, Division or Center which is responsible for oversight of this research study:**

U of Pgh | School of Medicine | Radiology

CS3.5 **Telephone Number of Principal Investigator:**

412-647-5176

CS3.6

Recorded Current E-mail Address of Principal Investigator to which all notifications

will be sent:

narendranr@upmc.edu

CS3.7 **Fax Number:**

412-647-0700

CS3.8 **Does this study include any personnel from Carnegie Mellon University, and/or use any CMU resources or facilities (e.g., Scientific Imaging and Brain Research Center (SIBR)?**

* No

CS3.9 **Is this your first submission, as PI, to the Pitt IRB?**

* No

[reviewer notes¬]

CS4.0

List of Co-Investigators:

Last	First	Organization
Mason	Neale	U of Pgh | School of Medicine | Radiology
Mountz	James	U of Pgh | School of Medicine | Radiology

[reviewer notes¬]

CS5.0 **Name of Primary Research Coordinator:**

Savannah Tollefson

CS5.1

Address of Primary Research Coordinator:

UPMC Presbyterian
PUH-B 938
200 Lothrop Street
Pittsburgh, PA 15213

CS5.2

Telephone Number of Primary Research Coordinator:

412-586-9888

CS6.0

Name of Secondary Research Coordinator:

Rehima Jordan

CS6.1 **Address of Secondary Research Coordinator:**

UPMC Presbyterian
PUH-B 938
200 Lothrop Street
Pittsburgh, PA 15213

CS6.2 **Telephone Number of Secondary Research Coordinator:**

412-246-5829

CS6.3 **Key Personnel/Support Staff (Only list those individuals who require access to OSIRIS):**

Last	First	Organization
Antonetti	Kathie	U of Pgh | School of Medicine | Radiology
Flanigan	Margaret	U of Pgh | School of Medicine | Radiology
Gertler	Josh	U of Pgh | School of Medicine | Radiology
Himes	Michael	UPMC | Hospital Divisions | Presbyterian/Shadyside | Radiology
Ruszkiewicz	James	U of Pgh | School of Medicine | Radiology
Stoughton	Clara	U of Pgh | School of Medicine | Radiology
Tollefson	Savannah	U of Pgh

[reviewer notes¬]

CS7.0 **Will this research study use any Clinical and Translational Research Center (CTRC) resources?**

No

[reviewer notes¬]

CS8.0 **Select the entity responsible for scientific review.**

External Scientific Review Completed – The **scientific merit of this research protocol has been confirmed** by an external scientific review committee as a condition of funding.

[reviewer notes¬]

CS9.0 **Does this research study involve the administration of an investigational drug or an FDA-approved drug that will be used for research purposes?**

* Yes

CS9.1

Do you plan to utilize the Investigational Drug Service (IDS) to dispense the drug?

* Yes

CS10.0 **Is this research study being conducted under a University of Pittsburgh-based, sponsor-investigator IND or IDE application?**

* No

If YES, you are required to submit the IND or IDE application and all subsequent FDA correspondence through the Office for Investigator-Sponsored IND and IDE Support (O3IS). Refer to applicable University policies posted on the O3IS website (www.O3IS.pitt.edu).

[reviewer notes¬]

CS11.0

Use the 'Add' button to upload one or more of the following:

- **the sponsor protocol (including investigator initiated studies) and/or other brochures**
- **the multi-center protocol and consent form template, *if applicable***

Name Modified Date

Is this research study supported in whole or in part by industry? This includes the provision of products (drugs or devices).

* No

Is this a multi-centered study?

* No

[reviewer notes¬]

CS12.0

Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation?

* Yes

HUSC GUIDANCE
REQUIREMENTS FOR THE REVIEW OF HUMAN SUBJECT RESEARCH PROTOCOLS BY THE
HUMAN USE SUBCOMMITTEE (HUSC), RADIATION SAFETY COMMITTEE

(effective 7/1/2018)

For Research Protocols Involving the Use or Evaluation of **Diagnostic or Therapeutic Procedures** that Emit Ionizing Radiation:

- Formal HUSC review/approval is required if the:

1. research protocol involves the use or the evaluation (i.e., for safety and/or effectiveness) of a radioactive agent or a device that is not currently FDA-approved for commercial marketing; including radioactive drugs or devices that are the subject of a FDA-accepted IND or IDE application or approved for clinical investigations under the FDA's Radioactive Drug Research Committee (RDRC) process. [1]
2. research protocol addresses (i.e, in the objectives or specific aims) the evaluation (i.e., for safety and/or effectiveness) or involves the use of a FDA-approved radiopharmaceutical or device-associated procedure for an "experimental" indication or using "experimental" procedures (i.e., an indication or procedures that are not consistent with standard clinical practice or the current FDA-approved product labeling). [1]
    - Note: HUSC review/approval is not required for research protocols that involve the use of diagnostic procedures being performed, in a manner and frequency that are consistent with standard clinical practice, for subject screening or to evaluate the outcome of a treatment regimen. This would include diagnostic procedures for off-label uses that are routinely performed in clinical practice. [1,2,3]
    - Note: HUSC review/approval is not required for research protocols that involve the use of therapeutic procedures being performed in a manner and frequency that is consistent with standard clinical practice. [1,2,3]
3. research protocol involves the enrollment of individuals (e.g., healthy volunteers) who will not be undergoing the procedure in association with the diagnosis or treatment of a disease or condition. [1]

For Humanitarian Use Devices:

- Formal HUSC review/approval is required for all Humanitarian Use Devices that emit ionizing radiation.

For any questions related to these requirements or their application, contact the Chair of the HUSC (412-647-0736) or the University's Radiation Safety Officer (412-624-2728).

[1] All research protocols wherein the parameters (e.g., dose, dosing frequency) for performing the procedure(s) that emit ionizing radiation are defined in the protocol must include an Authorized User (i.e., a physician or dentist who has expertise and who is credentialed in the respective medical specialty) as a listed co-investigator; i.e., so as to ensure adequate notification and respective compliance with the protocol.
[2] The risks of radiation exposure associated with the diagnostic or therapeutic procedure must continue to be addressed in the protocol and consent form using the standard, HUSC-accepted wording. (For diagnostic procedures refer to the University Human Research Protection Office website – www.hrpo.pitt.edu: A-Z Guidance/Radiation Guidance. For therapeutic procedures, address the specific risks currently known to be associated with the respective procedure.
[3] The University of Pittsburgh IRB, at its discretion, may request formal HUSC review of the research protocol.

CS12.1

After reviewing the HUSC guidance above, does your research protocol require HUSC review? (Note: University of Pittsburgh's Radiation Safety Committee oversight is

limited UPMC Presbyterian-Shadyside, Magee Women's Hospital of UPMC, Children's Hospital of Pittsburgh-UPMC, and Hillman Cancer Center. If other sites, you will be required to obtain approval from your radiation safety officer. Please contact askirb@pitt.edu for more information.)

Yes

Upload Radiation Forms:

Name	Modified Date
Narendran NOP Corticotropin	3/16/2016 3:08 PM
Updated dosimetry Table	3/30/2016 8:29 PM

CS13.0 Does this research study involve the deliberate transfer of recombinant or synthetic nucleic acid molecules into human subjects?

* No

Upload Appendix M of NIH Guidelines:

Name	Modified Date

CS14.0 Are you using UPMC facilities and/or UPMC patients during the conduct of your research study?

* Yes

If Yes, upload completed Research Fiscal Review Form:

Name	Modified Date
FRIAR PRO16030242.docx	3/18/2016 3:25 PM

[reviewer notes¬]

CS15.0 Indicate the sites where research activities will be performed and/or private information will be obtained.

Choose all sites that apply and/or use **Other** to include sites not listed:

Sites:
University of Pittsburgh
UPMC

University of Pittsburgh

Campus:

Main Campus - Pittsburgh

List university owned off-campus research sites if applicable:

UPMC

Sites:
UPMC Presbyterian
UPMC Western Psychiatric Institute & Clinic

If you selected **School**, **International** or **Other**, list the sites:

***For research being conducted at non Pitt or UPMC sites, upload a site permission letter granting the researcher permission to conduct their research at each external site:**

Name	Modified Date

CS15.1 Have you, Rajesh Narendran , verified that all members of the research team have the appropriate expertise, credentials, and if applicable, hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB protocol?

* Yes

CS15.2

Describe the availability of resources and the adequacy of the facilities to conduct this study:

* UPMC Presbyterian MRI Center: for MR scans.
UPMC Presbyterian PET Center: for PET scans, protected servers for data security, storage and distribution of data and biologic samples.
PET Office Space: for screening patients and controls.
UPMC Prebyterian University Hospital ED: for medical emergency management that may arise in subjects during conduct of research.

[reviewer notes¬]

CS16.0 Special Research Subject Populations:

Categories
None

[reviewer notes¬]

CS17.0 Does your research involve the experimental use of any type of human stem cell?

* No

[reviewer notes¬]

NIH Definition of a Clinical Trial

A research study[1] in which one or more human subjects[2] are prospectively assigned[3] to one or more interventions[4] (which may include placebo or other control) to evaluate the effects of those interventions on health related biomedical or behavioral outcomes.[5]

[1] See Common Rule definition of research at 45 CFR 46.102(d) .

[2] See Common Rule definition of human subject at 45 CFR 46.102(f) .

[3] The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

[4] An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

[5] Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

CS18.0 * Based on the above information, does this study meet the NIH definition of a clinical trial?

(•) **Yes** ( ) No

If Yes, click Save and then Click Here For Study Team's CITI Training Records . Please ensure all personnel's training is up to date

	Section: Section 1 - Objective, Aims, Background and Significance

[reviewer notes¬]

1.1 Objective: What is the overall purpose of this research study? (Limit response to 1-2 sentences.)

To develop an imaging methodology to examine corticotropin-releasing factor (CRF)-nociceptin receptor (NOP) interactions in humans.

1.2 Specific Aims: List the goals of the proposed study (e.g., describe the relevant hypotheses or the specific problems or issues that will be addressed by the study).

Aim 1: To determine if [C-11]NOP-1A receptor binding (VT) can be altered by an intravenous hydrocortisone (cortisol) challenge through CRF-NOP interactions.

In rodents, an injection of CRF into the lateral cerebroventricle results in increased NOP receptor expression (Rodi et al., 2008). We will test the existence of such an interaction in 20 healthy human subjects by measuring [C-11]NOP-1A VT under control conditions and following the administration of intravenous cortisol (hydrocortisone, 1 mg/kg). Note: Intravenous CRH is not used as a challenge, because it is not transported from the blood to the brain (Martins et al., 1996). Intravenous hydrocortisone (1mg/kg) will be used as the challenge, because in vivo microdialysis studies in sheep have demonstrated that it can cross the blood-brain barrier and increase CRF levels in the amygdala by ~ 200% (Cook, 2002; Schwartz et al., 1972). Hydrocortisone increases amygdala CRF levels via its action on type 2 glucocorticoid receptors (Cook, 2002).

The hypothesis is that hydrocortisone-induced increases in amygdala CRF will result in higher [C-11]NOP-1A VT. This would suggest that transmission at NOP receptors is increased to counteract hydrocortisone's activation of CRF and the brain stress system. If successful, future studies will be proposed with this hydrocortisone- [C-11]NOP-1A PET imaging paradigm to examine CRF-NOP interactions in addictive disorders.

1.3 Background: Briefly describe previous findings or observations that provide the background leading to this proposal.

A1. Nociceptin: a functional CRF antagonist

The endogenous neuropeptide, nociceptin, and its target NOP receptor are structurally similar to dynorphin A and its target kappa opioid receptors (Meunier et al., 1995; Reinscheid et al., 1995). However, nociceptin has no affinity for the classical mu, kappa and delta opioid receptors, and endogenous opioids, such as endorphins, enkephalins, dynorphin, etc., do not bind to the NOP receptor. Nociceptin and neuropeptide Y are postulated to be components of an anti-stress system in the brain that counteracts stress and anxiety, which is typically mediated by CRF, norepinephrine, orexin, vasopressin and dynorphin (Koob, 2008). Consistent with this notion, nociceptin has been shown to block stress-induced analgesia, anorexia, and anxious behaviors in rodents (Ciccocioppo et al., 2002; Jenck et al., 1997; Mogil et al., 1996). Also, nociceptin knockout mice show increased anxiety-like behaviors and are unable to adapt to repeated stress, compared to wild-type mice (Koster et al., 1999).

Nociceptin also has no appreciable affinity for CRF receptors. However, nociceptin has been shown to oppose the functions of extra-hypothalamic CRF and, thus, exert an anti-stress effect (Ciccocioppo et al., 2004a). Studies have convincingly demonstrated that the administration of nociceptin in the extended amygdala inhibits CRF -induced anorexia and anxiety-like symptoms in rodents (Ciccocioppo et al., 2002; Ciccocioppo et al., 2004a; Ciccocioppo et al., 2003; Ciccocioppo et al., 2001; Rodi et al., 2008). Furthermore, studies that have evaluated restraint-

stress in rodents show an ~ 70% increase in NOP receptor protein expression in the extended amygdala to counteract increases in CRF (Ciccocioppo et al., 2014a). This increase in NOP receptor expression is detectable in animals ~ 6 hours following exposure to restraint stress. However, this increase in NOP receptors is not detectable 20 minutes following restraint stress (personal communication with Dr. Ciccocioppo), and is not accompanied by changes in the endogenous nociceptin (Ciccocioppo et al., 2014a). This suggests that the restraint-stress induced increase in amygdala NOP receptors is not due to endogenous competition between the ligand and the receptor site, but rather indicative of new receptor synthesis or recycling of internalized receptors to the cell membrane. Increased NOP receptor expression is likely an adaptive response to stress. Consistent with this nociceptin has been shown to block CRF-induced increases in GABAA mediated inhibitory postsynaptic potential (IPSP) more strongly in restraint stress animals with increased NOP receptors compared to control animals (Ciccocioppo et al., 2014a). In a more direct documentation of CRF-NOP interactions, an injection of CRF into the lateral cerebroventricle led to a 2-fold increase in NOP receptor expression in the bed nucleus of the stria terminalis (BNST) after six hours (Rodi et al., 2008). Again, consistent with the notion that increased NOP receptor expression is an adaptive response to increased CRF/stress, an injection of nociceptin into the BNST (or lateral cerebroventricle) blocked CRF-induced anxiety-like behaviors (Rodi et al., 2008). Based on these data, it is tempting to speculate that abnormal CRF-NOP interactions underlie the anxiety-like symptoms in several psychiatric and addictive disorders. For example, it is possible that the inability to effectively upregulate NOP receptors to counteract increased CRF in stress-related conditions might be predictive of risk and relapse in alcoholism. It may also be predictive of risk for anxiety disorders such as post-traumatic stress disorder –another disorder in which both the CRF and NOP receptors have been implicated (Zhang et al., 2012). Finally, there are other non-CRF mediated mechanisms that contribute to the anti-stress effects of nociceptin as well. They include its ability to modulate the release of multiple neurotransmitters including dopamine, serotonin, acetylcholine, glutamate and GABA via stimulation of NOP receptors that are located pre-synaptically on the axon terminals of these neurons (Schlicker and Morari, 2000). These non-CRF mechanisms will not be the focus of this application.

A2. CRF-NOP interactions: relevance in addiction

The three phases of addiction are intoxication, withdrawal and craving. In contrast to dopamine release that drives positive reinforcement in the intoxication phase, an imbalance between the brain stress (CRF, orexin, vasopressin and dynorphin) and anti-stress systems (neuropeptide Y and nociceptin) has been postulated to drive negative reinforcement in the withdrawal and craving phases (Koob, 2008). Studies by Koob and colleagues have demonstrated that neurotransmitters in the brain stress and anti-stress systems work in series or in parallel in the extended amygdala to impact emotional states and contribute to relapse. Within the extended amygdala, stress-mediators such as CRF increase GABAA inhibitory post-synaptic potentials (IPSCs), whereas anti-stress mediators such as nociceptin decrease GABAA IPSCs (Roberto and Siggins, 2006). Because most neurons in the extended amygdala are GABA-ergic inhibitory interneurons or projection neurons, the GABA-ergic tone in this region regulates the flow of information through the intra-amygdala circuits. This in turn influences both local and output neurons to downstream regions that mediate a behavioral response. To summarize, stimulation of CRF receptors: increases GABA transmission in the extended amygdala; promotes anxiety-like behaviors; and increases alcohol consumption (Roberto et al., 2010). In contrast, stimulation of NOP receptors: blocks CRF-induced increases in GABA transmission in the extended amygdala; diminishes anxiety; and prevents conditioned reinstatement in animals that self-administer alcohol (Ciccocioppo et al., 2014a; Ciccocioppo et al., 2004b; Cruz et al., 2012; Rodi et al., 2008). These basic studies have led investigators to postulate a therapeutic role for increasing transmission at NOP receptors to counteract an overactive CRF system and, by extension, block negative reinforcement and stress-induced relapse in alcoholism (Witkin et al., 2014). Furthermore, intracerebroventricular administration of nociceptin has also been shown to

attenuate positive reinforcement by reducing mesolimbic DA release following a drug reward (cocaine and morphine). Microdialysis studies have demonstrated decreased cocaine- and morphine- induced DA release in the nucleus accumbens following intra- ventral tegmental area (VTA) and intra-nucleus accumbens nociceptin administration (Di Giannuario and Pieretti, 2000; Di Giannuario et al., 1999; Lutfy et al., 2001; Murphy et al., 1996; Vazquez-DeRose et al., 2013). It is likely that nociceptin directly modulates midbrain DA neurons to impact DA release because 50-90% of tyrosine hydroxylase positive cells (TH +) in the VTA (and substantia nigra) express NOP receptors (Maidment et al., 2002; Norton et al., 2002). Alternatively, an effect for pre-synaptic NOP receptors on DA terminals cannot be ruled out because administration of nociceptin into the nucleus accumbens reduces DA release as well (Vazquez-DeRose et al., 2013). The mechanisms by which nociceptin can both block negative reinforcement via CRF antagonism and attenuate positive reinforcement via reduction in mesolimbic DA transmission in rodent addiction models make it an attractive therapeutic target to pursue in human addicts. Increased transmission at NOP receptors not only blocks the rewarding properties of alcohol in the conditioned place preference behavioral paradigm (Ciccocioppo et al., 1999; Kuzmin et al., 2009), but also reduces alcohol consumption (Ciccocioppo et al., 1999). It is also effective in preventing the somatic and affective signs of alcohol withdrawal in alcohol-dependent rodents during both acute and protracted withdrawal (Economidou et al., 2011). Highly relevant to the clinic is its ability to block cue- and stress-induced alcohol reinstatement following prolonged abstinence in rodent models of alcoholism (Ciccocioppo et al., 2004b; Martin-Fardon et al., 2000). Most of the aforementioned studies were conducted in rodents that prefer and consume large amounts of alcohol. These alcoholic animals demonstrate increased NOP receptor expression (mRNA) and receptor density (Bmax) in the extended amygdala, ventral tegmental area (VTA), and cortex compared to controls (Economidou et al., 2008). Thus, it is tempting to speculate that an increase in NOP receptors in alcohol-preferring rodents is a compensatory adaptation to increased CRF and related stress in alcoholism. This is supported by studies that show increasing NOP receptor mediated transmission by an injection of nociceptin into the CeA will suppress alcohol self-administration (Economidou et al., 2008; Gustafsson et al., 2005). The only human study to date that has evaluated NOP receptors in postmortem brains found a 1.4-fold reduction in NOP receptor mRNA in the CeA in alcoholics compared to controls (Kuzmin et al., 2009). No such differences were evidenced in the hippocampus and prefrontal cortex. These human data are in sharp contrast to the upregulation of NOP receptors reported in alcohol preferring rodents. The exact reasons for the discrepancy between rodent and human results with respect to NOP receptor gene expression are unclear. One possibility is that decreased NOP receptor expression may indicate a failure to adequately compensate for increased CRF transmission in human alcoholics with more severe and chronic disease relative to that in the alcohol-preferring rodents. This would indicate a more effective compensatory upregulation of NOP receptors in response to increased CRF transmission in alcohol-preferring rodents. Finally, the importance of abnormalities in nociceptin and NOP receptors is further highlighted by data from genetic studies that support a link between alcoholism and polymorphisms in the genes encoding for them (Huang et al., 2008; Xuei et al., 2008). A major gap in the existing addiction literature is that no in vivo methodology exists to examine CRF-NOP interactions. Thus, the development of a methodology to examine CRF-NOP interactions in vivo in the living human brain will have a major impact in understanding addictive disorders in which stress is linked to relapse.

A3. Imaging of NOP receptors with [C-11]NOP-1A and PET

In a major advancement, the imaging group at NIMH recently radiolabeled and successfully validated a NOP receptor antagonist radiotracer [C-11] (S)-3-(2'-fluoro-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran]-1-yl)-2-(2-fluorobenzyl)-N-methylpropanamide (NOP-1A) for use in humans (Pike et al., 2011). [C-11]NOP-1A binds with relatively high affinity to NOP receptors (KD, 0.15 nM). [C-11]NOP-1A total uptake in various brain regions (VT) is consistent with the known distribution of NOP receptors in human and primate brain (relatively

high density in amygdala, striatum and cerebral cortex; and moderate density in cerebellum and midbrain) (Berthele et al., 2003; Bridge et al., 2003; Kimura et al., 2011; Lohith et al., 2012). Blocking studies in primates with the specific NOP receptor antagonist SB-612111 (KD 0.33 nM, 1mg/kg intravenously) indicate that 50-70% of [C-11]NOP-1A VT in brain regions represents specific binding to NOP receptors (Kimura et al., 2011). [C-11]NOP-1A demonstrates desirable pharmacokinetics in humans: brain uptake peaks relatively quickly (~ 10 min) and washes out rapidly; brain data is modeled well by a 2-tissue compartment kinetic analysis; VT values in brain regions range from 7 to 15; VT remains stable following 70 min of data acquisition; and the test-retest variability for VT is an acceptable ≤ 15% in all brain regions (Lohith et al., 2014; Lohith et al., 2012).

[C-11]NOP-1A has been administered to approximately 50 subjects at the University of Pittsburgh PET facility by the PI in his prior research studies. Subject populations that it has been administered to include healthy subjects, alcoholics, cocaine addicts and PTSD subjects. To date no adverse reactions have been reported with its use.

A4. Summary: A wealth of pre-clinical literature implicates the stress and anti-stress neuropeptides CRF and nociceptin in negative reinforcement and relapse in alcoholism. If the proposed experiments were successful in showing increased NOP receptor binding in response to greater amygdala CRF levels induced by a hydrocortisone challenge, this would support the use of this imaging paradigm to examine in vivo interactions between CRF and NOP in humans. Such results would have far reaching implications in efforts to characterize the brain stress and anti-stress systems in addiction (Koob, 2008)., and other psychiatric disorders (e.g., post-traumatic stress disorder, major depression, etc.,). Characterizing CRF-NOP interactions in humans with drug and alcohol use disorders is an important step in informing the field of the therapeutic potential for CRF antagonist and NOP agonist medications to treat addiction. For example, if we show that there is a smaller compensatory increase in NOP receptors in response to CRF release in alcoholics compared to controls, this would support the clinical development of novel NOP agonist compounds (MT-7716 and Ro 64-6198) that have shown promise in rodent models of alcoholism (Ciccocioppo et al., 2014b; de Guglielmo et al., 2014; Kallupi et al., 2014; Kuzmin et al., 2007).

1.4 Significance: Why is it important that this research be conducted? What gaps in existing information or knowledge is this research intended to fill?

A major gap in the existing addiction literature is that no in vivo methodology exists to examine the interactions between corticotropin-releasing factor and nociceptin receptors in humans. The availability of an imaging paradigm to examine these interactions would have far reaching implications in characterizing the role of stress and anti-stress neuropeptides in addiction and other psychiatric disorders.

	Section: Section 2 - Research Design and Methods

[reviewer notes¬]

2.1 **Does this research study involve the *use* or evaluation of a drug, biological, or nutritional (e.g., herbal or dietary) supplement?**

* Yes

2.1.1 **Does this research study involve an evaluation of the safety and/or effectiveness of one or more marketed nutritional (e.g., herbal or dietary) supplements for the diagnosis, prevention, mitigation or treatment of a specific disease or condition or symptoms characteristic of a specfic disease or condition?**

* No

[reviewer notes¬]

2.1.2 **Does this research study involve the use or evaluation of one or more drugs or biologicals not currently approved by the FDA for general marketing?**

* Yes

2.1.2.1 **List each of the unapproved drugs or biologicals being used or evaluated in this research study.**

Specify for each listed drug or biological the corresponding IND number, HUSC (RDRC) number (for applicable radioactive drugs):

	Drug/biologic	IND #	HUSC #
View	[C-11]NOP-1A		HUSC 0725

[reviewer notes¬]

2.1.3 **Does this research involve the *use* or an evaluation of the effectiveness and/or safety of one or more drugs or biologicals currently approved by the FDA for general marketing?**

* Yes

2.1.3.1 **Are the FDA-approved drugs or biologicals being evaluated in this research study for a new clinical indication, different population, or route of administration and/or dosage level that is not currently specified in the FDA-approved product**

labeling?

Drugs are often used **Off-Label** during routine practice. Before answering this question, review the FDA product labeling (http://labels.fda.gov) for the approved "Indications and Usage." If being used off-label, answer **Yes** to this question**.** You are required to provide information and/or upload the package insert for each drug that is administered for research purposes.

* Yes

If you respond **YES**, an IND number or the FDA written concurrence of IND exemption may be required.

2.1.3.1.1

By using the "Add" button available below, list and specify the following for <u>each</u> of the FDA-approved drugs or biologicals being evaluated under this research study.

- Whether data from this research will be reported to the FDA in support of a new indication for the use of this drug product or to support any other significant change in the labeling (i.e., new indication). If **Yes**, provide the corresponding IND number.
- Whether data from this research will be used to support a significant change in the advertising for this drug product (i.e., new advertisement). If **Yes**, provide the corresponding IND number.
- Whether the proposed 'off-label' evaulation of the approved drug is felt to significantly increase the risks (or decrease the acceptability of risk) compared to the current approved uses of this drug or biological. If **Yes**, provide the corresponding IND number. If **No**, provide a justification for why the risk is not increased or the acceptablity of risk is not decreased (i.e., risk justification).

Approved Drug/Biologic	New Indication	New Advertisement	Risk Concern	Risk Justification/No IND	IND #
			Hydrocortisone IV is approved by the FDA for a variety of medical indications: IV Hydrocortisone (solut-cortef) is FDA approved to be administered to (1) Allergic states: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions. (2) Dermatologic diseases: Bullous dermatitis		

				herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome). (3) Endocrine disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis. (4) Gastrointestinal diseases: To tide the patient over a critical period of the disease in regional enteritis (systemic therapy) and ulcerative colitis. (5) Hematologic disorders: Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond-Blackfan anemia), idiopathic thrombocytopenic purpura in adults (intravenous administration only; intramuscular administration is contraindicated), pure red cell aplasia, selected cases of secondary thrombocytopenia. (6) Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy. (7) Neoplastic diseases: For the palliative management of leukemias and lymphomas. (8) Nervous System: Acute exacerbations of multiple sclerosis; cerebral edema associated with	
View	Intravenous hydrocortisone	no	no		IV hydrocortisone has been administered to healthy humans in a off-label manner at doses ≤ 200 mg with no serious side effects in several previous research studies (Jung et al., 2014; Symonds et al., 2012; Wachtel et al., 2001; Wachtel and de Wit, 2001). Thus, in administering hydrocortisone 1 mg/kg IV to

	primary or metastatic brain tumor, or craniotomy. (9) Ophthalmic diseases: Sympathetic ophthalmia, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids. (10) Renal diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus. (11) Respiratory diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis. (12) Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, temporal arteritis, polymyositis, and systemic lupus erythematosus. In this study, we propose to administer hydrocortisone at a dose of 1mg/kg, IV, (i.e., < 100 mg because our subjects typically weight 70-100 Kgs) to healthy controls to evaluate interactions between CRF and nociceptin receptors. This is far below the FDA approved maximum IV dose of 500 mg. Thus, it should not significantly increase (or decrease the acceptability of risk) compared to currently	healthy controls the risk is not increased or acceptability of risk is not decreased

approved uses.

Upload information on FDA approved indications/doses and FDA exemption letter if applicable:

Name	Modified Date
Solu-Cortef package insert.pdf	3/30/2016 3:56 PM

[reviewer notes¬]

2.2 Will this research *use* or evaluate the safety and/or effectiveness of one or more devices?

* No

[reviewer notes¬]

2.3 Summarize the general classification (e.g., descriptive, experimental) and methodological design (e.g., observational, cross-sectional, longitudinal, randomized, open-label single-blind, double-blind, placebo-controlled, active treatment controlled, parallel arm, cross-over arm) of the proposed research study, as applicable.

experimental, open-label

2.3.1 Does this research study involve a placebo-controlled arm?

* No

[reviewer notes¬]

2.4 Will any research subjects be withdrawn from known effective therapy for the purpose of participating in this research study?

* No

[reviewer notes¬]

2.5 Will screening procedures (i.e., procedures to determine research subject eligibility) be performed specifically for the purpose of this research study?

* Yes

2.5.1 List the screening procedures that will be performed for the purpose of this research study. Do NOT include the inclusion/exclusion criteria in this section as they will be addressed in section 3; questions 3.13 and 3.14.

Pre-study visit screening procedures (~6 hours)
Once the written consent has been obtained, all potential participants will undergo a clinical evaluation, which takes approximately 6 hours to complete and may be done on separate days. The testing consist of the following:

(1) PET facility screening form to ensure subjects can undergo PET and MRI scans.

(2) Psychiatric evaluation: Structured Clinical Interview for DSM-5 (SCID 5 – research version) will be used to determine psychiatric diagnoses; As subjects are healthy controls they will only receive the SCID 5 screening modules (this is the non-patient version). If there is a clinical suspicion based on these screening modules that the subject may have alcohol use disorder or cannabis use disorder, or psychosis or major depression, etc., the corresponding modules may be done to exclude these disorders in healthy controls. The need to do these corresponding modules will be performed at the PI's discretion based on his review of the screening module; Time needed: 2 hours

(3) Medical evaluation: We will do a routine physical examination (15 to 20 minutes) and a medical evaluation with laboratory tests, e.g., EKG, VS, hemoglobin, hematocrit, total leukocyte with differential, plasma electrolytes, BUN/Cr, liver and thyroid function (TSH level), urinalysis and toxicology, and serum pregnancy for female subjects of child bearing potential (i.e., females who have not undergone a surgical sterilization procedure or who are not at least one year post-menopausal).
Medical test results will be reviewed prior to study entry. The laboratory tests will not be repeated if they have been performed within the past six months. [Note that the serum pregnancy test, and urine toxicology prior to PET scans will not fall into this category]. In addition, other study measures such as MRIs and cognitive tasks will not be repeated if they have been performed under another IRB approved Psychiatric Molecular Imaging Program (PMIP) protocol within the past 6 months.

(4) Stress and anxiety rating scales:
(a) Perceived stress scale (PSS) (Cohen et al., 1983): A 14-item scale that measures the degree to which situations in an individual's life are appraised as stressful.
(b) Hamilton Anxiety Rating Scale (HAM A) (Hamilton, 1959): A 14-item scale that measures anxiety-like symptoms.
(c) Center for Epidemiological Studies in Depression (CES-D): A 20 item scale that measures depression.

The records of the subjects who fail screening after signing consent are not destroyed, but maintained as any subject who continues the research study with the reason for exclusion mentioned in it.

All clinical assessments, including the SCID will be administered by research coordinators and co-investigators as delegated by the PI. The PI will supervise the research coordinators till they are deemed competent to do it on their own; He will also assist them as questions arise in the future.

Screening procedures may be done after initiation or completion of the experimental procedures

depending on MRI and PET schedules because this is a study that involves healthy controls. For example, rating scales such as HAM-A, PSS, CES-D, etc., that do not determine a subject's inclusions/exclusion may be done on the day, or even after scans. It may also involve doing a MRI before labs, if the subject has no contraindications on the PET/MRI screening. However, a PET will not be done before completion of the SCID and labs because they are necessary to rule out low hemoglobin, current psych and drug use disorders etc.)

[reviewer notes¬]

2.6

Provide a detailed description of all research activities (e.g., all drugs or devices; psychosocial interventions or measures) that will be performed for the purpose of this research study.

This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.

At a minimum the description should include:

- **all research activities**
- **personnel (by role) performing the procedures**
- **location of procedures**
- **duration of procedures**
- **timeline of study procedures**

All study assessments, and evaluations will be done for research purposes (including any clinical research) with nothing that falls into the category of 'clinical care'. In this research, subjects will be studied as detailed below.

DRUG/DEVICE INFORMATION

I). [C-11]NOP-1A
[C-11]NOP-1A is not approved by the FDA for routine clinical use. However, its use in this research study is considered to be generally safe and effective as determined by the University of Pittsburgh Radioactive Drug Research Committee (RDRC) in accordance with FDA regulations. [C-11]NOP-1A will be prepared according to the information and protocols described in the respective Drug Master File approved by the University of Pittsburgh Radioactive Drug Research Committee. The amount of radioactivity injected for [C-11]NOP-1A will be 12 mCi/scan based on previously published reports (Lohith et al., 2012). A radioactive dose of approximately 12 mCi will provide adequate signal to noise ratio to quantify NOP receptors (Lohith et al., 2012). [C-11]NOP-1A has been previously administered to humans and documented to have “no pharmacological effects” at the mass dose levels that will be administered (Note: the mass limits for this study will be the same as in RDRC approved Drug Master File for [C-11]NOP-1A).

II). Intravenous Hydrocortisone, (Solu-Cortef ®)
Intravenous hydrocortisone is Food and Drug Administration (FDA) approved for steroid-responsive disorders (e.g., inflammation, status asthmaticus, acute adrenal insufficiency, etc.) when oral therapy is not feasible. The hydrocortisone dose and route of administration that we

propose in this research protocol is consistent with the use recommended in its package insert information (Solu-Cortef®, package insert, http://www.pdr.net/drug-summary/solu-cortef?druglabelid=1880#3). The proposed dose of hydrocortisone (1mg/kg, IV, i.e., ≤ 100 mg) that will be used in this imaging study is far below the FDA approved maximum IV dose of 500 mg. In previously published research studies, IV hydrocortisone has been administered to healthy humans at doses ≤ 200 mg with no serious side effects (Jung et al., 2014; Symonds et al., 2012; Wachtel et al., 2001; Wachtel and de Wit, 2001). Intravenous hydrocortisone 1 mg/Kg will be formulated as listed in the FDA package and dispensed in a final volume of 50mL normal saline by the Investigative Drug Service (IDS).

STUDY DAYS (EXPERIMENTAL PROCEDURES)
No more than 6 months will be allowed to elapse between the pre-study visit and study visit.

The study will take place over approximately 3 experimental days.

The subject will receive a venous line for infusion of the radiopharmaceutical and an arterial line for blood sampling.

The entire PET/CT scanning session will require about 8 hours to complete while the study day could last as long as 10 hours (if the MR and PET are done in the same day).

In the unlikely event that the experimental PET/CT procedures cannot be completed in a single day (due to a non-functional MRI scanner, PET camera or cyclotron or any other unavoidable reason), the subject may be given the option to return within 30 days to complete the study. On this “completion” day, participant preparation again consists of intravenous and arterial catheterization. The scanning protocol will continue from the point that the protocol was aborted on the initial day. No subject will receive more than 2-3 low-dose CT scans, two [C-11]NOP-1A PET scans and one hydrocortisone challenge, regardless of whether the study is completed in one or two days. That is, the total radiation exposure over the two-PET scanning days will not be significantly greater than if the entire procedure had been completed in one day, however the participant would receive an additional intravenous, arterial catheterization, low-dose CT scan and additional urine drug and pregnancy screens.

All tests for this research study will be performed at either the MR Research Center (MRRC) on the 8th floor of UPMC Presbyterian University Hospital (PUH) or the PET Facility on the 9th floor of UPMC PUH (directly above the MRRC).

The goal of the study is to determine if [C-11]NOP-1A receptor binding (VT) can be altered by an intravenous hydrocortisone (cortisol) challenge through CRF-NOP interactions. Twenty heathy control subjects will be studied twice with [C-11]NOP-1A before and after an intravenous hydrocortisone challenge (1 mg/Kg).

SPECIFIC METHODS AND DESIGN

I). MRI Protocol
Structural MRI: All female participants will undergo a urine pregnancy test prior to MRI. Subjects will undergo an MRI procedure for anatomical localization of regions-of-interest (ROI). Participants with a questionable history of metallic fragments will not be included in the study. A single MRI study will be performed prior to the first PET study. The MRI examinations will be conducted on the 8th floor in the UPMC MRRC, which is located directly below the PET Facility, using a 3T scanner. A volumetric MPRAGE sequence will provide the anatomical framework for ROI analysis. This sequence is optimized to maximize the contrast among gray matter, white matter, and cerebral spinal fluid and provides high-resolution delineation of cortical and

subcortical structures. Imaging time for this pulse sequence is less than 8 minutes, with total time for the MRI scan estimated at 30 minutes. MRI data will be transferred to the PET Facility over the electronic network and co-registered with the PET data on a SUN Workstation using software routinely used for this purpose (Woods et al., 1992). The registered MRI will be used as an individualized anatomic map for the selection of ROIs used in the analysis of the PET data. The MRI might be obtained on the same day as a PET scan when possible to reduce transportation costs and inconvenience. Finally, the MRI will not be repeated if they have been performed under another IRB approved Psychiatric Molecular Imaging Program (PMIP) protocol within the past 6 months.

II). PET Protocol
PET scans will be acquired at the 9th floor PET Facility at UPMC PUH using a Siemens PET/CT (3D acquisition mode) scanner. Each participant will receive both a baseline [C-11]NOP-1A PET scan and post-hydrocortisone [C-11]NOP-1A PET scan following hydrocortisone administration in order to examine CRF-NOP receptor interactions.

Subject Preparation:

A). Baseline review of medical and medication history (to document no change from screening).

B). A urine pregnancy test is done on females of child bearing potential (i.e., females who have not undergone a surgical sterilization procedure or who are not at least one year post-menopausal) to confirm that pregnancy has not occurred between the time of the screening and the PET. In addition, a statement of use of a method of contraception for all subjects in the past 15 days (abstinence, barrier methods, oral contraceptive medications, etc.) is obtained.

C). A urine drug screen and alcohol breath analyzer to ensure the subject did not abuse any illicit drugs or alcohol prior to the PET scan (this test will occur prior to the placement of the venous and arterial catheters). Subjects will be informed that this test will occur.

D). The preparation of the subject will include the placement of a venous line and an arterial line. An anesthesiologist will place the arterial line. The purpose of these lines is as follows:

Arterial line (all subjects):
1. Blood sampling for [C-11]NOP-1A arterial concentration.
2. The arterial line will be placed after completion of the Allen test and infiltration of the skin with 1 to 2% lidocaine.
If the arterial line cannot be obtained for any reason, the PET study will NOT proceed as an arterial input function is necessary for the derivation of the primary outcome measure, total distribution volume (VT). Note: As the radiotracer [C-11]NOP-1A does not have a reference region (i.e., region devoid of NOP-1A specific binding), it is necessary to have the arterial input for appropriate quantitation of NOP-1A binding (Kimura et al., 2011).

Venous line (all subjects):
1. [C-11]NOP-1A (single bolus).

E). Blood pressure, heart rate and temperature will be documented prior to the PET scan.

F). Before the PET and CT scan procedures are initiated, a wrist band (Empatica, E4) will be placed on the subject's wrist that does not have the arterial line. This wrist band which looks similar to 'apple watch' will continuously monitor and record the subjects' heart rate, inter-beat interval, and electrodermal activity. Subjects will wear this wrist band till the completion of both their PET/CT scans.

G). A low-dose CT scan to correct the PET scan measurements for attenuation will be performed in a few minutes.

H). Following this CT scan, 12 mCi of [C-11]NOP-1A will be injected intravenously. Dynamic PET data will be collected for 70 min.

I). At the end of this scan, the subject will be a provided a brief (~5 to 10 min) break to relax out of the scanner.

J). Subjects will then be administered 1 mg/kg of intravenous hydrocortisone as a bolus over 90 seconds. Following this, subjects will be monitored by the investigative team for subjective and objective adverse events (see monitoring listed below).

K). A second low-dose CT scan and [C-11]NOP-1A scan will be acquired a minimum of 3.5-hours post hydrocortisone, identical to the methods outlined previously. The timing of the second [C-11]NOP-1A administration and subsequent PET scanning (i.e., ~ 3.5 to 4.5 hours) is based on previous basic science studies that have documented CRF-NOP interactions (Ciccocioppo et al., 2014a; Rodi et al., 2008). The proposed timing will also ensure that the maximum increase in amygdala cortisol and CRF (Tmax ~ 25 to 30 min) following intravenous hydrocortisone (1mg/kg) has occurred prior to the PET scan (Cook, 2002).

Blood Sampling during [C-11]NOP-1A PET scans: Periodic arterial blood sampling will be performed during the PET studies for the quantitative data analyses (i.e. measurement of the radiotracer and its metabolites in the blood). These blood draws will not exceed 130 ml (about 9 tablespoonfuls) of blood in total. For each PET scans, hand-drawn arterial blood samples (0.5 ml) will be collected throughout the scan with no more than 20 collected during the first 2 min and no more than 15 collected at intervals of increasing duration minutes (no more than 35 total samples). Also, larger blood samples (3-5 ml) will be obtained at no more than 8 times during each PET scan for the determination of radiolabeled metabolites and protein binding. This would amount to no more than 43 arterial samples and a blood volume loss of no more than 60 ml (4-5 tablespoonfuls)/scan (60 * 2 scans = 120 mL). In addition to this two 3-5 mL blood samples will be drawn for measuring cortisol plasma levels for each post-hydrocortisone scan (2 * 5* 1 scan =10 mL). The timing of these cortisol blood samples will be t=0 and 1h post-hydrocortisone

L). Following this scan, all subjects will receive:
1. Physical Exam.
2. Mental Status Exam.
3. EKG.
4. Vital Signs measurement.

M). The subject will be evaluated by a physician to ensure they meet the following discharge criteria:
1. a blood pressure of > 90/60 and < 150/90.
2. a heart rate > 50 or < 110.
3. no reported subjective or objective side effects from the hydrocortisone at discharge.
4. a normal EKG (or not clinically significant, or no change from baseline EKG as determined by a physician)
5. a normal physical exam.
6. a normal mental status exam.

N). Healthy control who meet the above listed criteria following the PET scans will be

discharged home.

SUBJECT MONITORING:

A). Subject monitoring prior to the PET Scan
1. A physician will review screening labs, EKG and medical evaluation (see attached) prior to scan day.
2. Baseline review of systems and medication history (to document no change from screening).
3. Vital signs.
4. Urine toxicology screen.
5. A statement of use of a method of contraception for all subjects in the past 15 days (abstinence, barrier methods, oral contraceptive medications, etc.).
6. All female subjects of child bearing potential will undergo urine pregnancy testing to rule out pregnancy on the day of the PET scans prior to any of the PET scanning procedures.

B). Subject monitoring during PET scans
1. An experienced technician will be in both visual and verbal contact with the participant at all times during the study. If the participant voices any difficulty or desires to be removed from the scanner, or if the technician sees any indication that the participant is experiencing discomfort, the participant will be immediately removed from the scanner and verbally reassured.

C). Subject monitoring on hydrocortisone
1. The hydrocortisone will be administered by a physician investigator familiar with the protocol. The physician investigator will also be available in the PET facility to monitor the subject on hydrocortisone.
2. Blood pressure and heart rate will be recorded once prior to hydrocortisone and following hydrocortisone every ten minutes for the first 60 minutes, then every 15 minutes thereafter (up to at least 120 min).
3. Subjects will be assessed once at baseline (time 0), once at 60 minutes post-hydrocortisone (t=60 min), and once before the second [C-11]NOP scan with visual analog scales such as the PSS, HAM-A and CES D (scales attached in 2.8) to evaluate their subjective feelings while on hydrocortisone.

2.6.1

Will blood samples be obtained as part of this research study?

* Yes

*If submitting a protocol for expedited review, it should be clear that the planned blood draws are within the parameters described here: http://www.hhs.gov/ohrp/policy/expedited98.html (see Expedited Research Category #2)

If **Yes**, address the frequency, volume per withdrawal, the total volume per visit, and the qualifications of the individual performing the procedure:
Blood Sampling During Screening (total 35mL):
During screening, approximately 30-35 ml of blood will be drawn for routine medical tests. This will be done only once.

Blood Sampling During PET Imaging (total 130 mL):
Periodic arterial blood sampling will be performed during the PET studies for the quantitative data analyses (i.e. measurement of the radiotracer and its metabolites in the blood). These blood draws will not exceed 130 ml (about 9 tablespoonfuls) of blood in total. For each PET

scan, hand-drawn arterial blood samples (0.5 ml) will be collected throughout the scan with no more than 20 collected during the first 2 min and no more than 15 collected at intervals of increasing duration minutes (no more than 35 total samples). Also, larger blood samples (3-5 ml) will be obtained at no more than 8 times during each PET scan for the determination of radiolabeled metabolites and protein binding. This would amount to no more than 43 arterial samples and a blood volume loss of no more than 60 ml (4-5 tablespoonfuls)/scan (60 * 2 scans = 120 mL). In addition to this, two 3 to 5 mL blood samples will be drawn for measuring cortisol plasma levels for each post-hydrocortisone scan (2 * 5* 1 scan =10 mL). The timing of these cortisol blood samples will be t=0 and t=60 min post-hydrocortisone challenge.

Thus, the cumulative amount of blood drawn for the screening and PET studies will be 165 mL (35 + 130 mL).

Study Flow Chart:

Name	Modified Date
Flow chart.xlsx	3/30/2016 9:39 PM

[reviewer notes¬]

2.7 Will follow-up procedures be performed specifically for research purposes? Follow-up procedures may include phone calls, interviews, biomedical tests or other monitoring procedures.

* Yes

Detailed procedures listed in the textbox below:

A follow-up telephone call will be made approximately 1 to 7 days after the last scan to the healthy control subjects to enquire about any adverse events he or she may have encountered related to the scans.

[reviewer notes¬]

2.8 Does this research study involve the use of any questionnaires, interview or survey instruments?

* Yes

Upload a copy of all materials except for the SCID or KSADS which are on file at the IRB. The use of all instruments must be addressed in question 2.6 and/or question 2.7 (except for an exempt submission where they should be addressed on the appropriate uploaded exempt form).

Name	Modified Date
PSS	3/11/2016 2:21 PM
CES-D.pdf	3/11/2016 2:20 PM
HAM-A	3/11/2016 2:21 PM

Previously the name and publisher for commercially available materials were listed in the textbox below but effective 9/1/2015, all materials (except for the SCID and KSADS) must be uploaded using the Add button above.

[reviewer notes¬]

2.9 **If subjects are also patients, will any clinical procedures that are being used for their conventional medical care also be used for research purposes?**

* no

If **Yes,** describe the clinical procedures (and, if applicable, their frequency) that will be used for research purposes:

2.10 The blood sample question was moved to 2.6.1.

[reviewer notes¬]

2.11 **What is the total duration of the subject's participation in this research study across all visits, including follow-up surveillance?**

* < 6 months

[reviewer notes¬]

2.12 **Does this research study involve any type of planned deception?**
If Yes, you are required to request an alteration of the informed consent process (question 4.7)

* No

[reviewer notes¬]

2.13 **Does this research study involve the use of UPMC/Pitt protected health information that will be de-identified by an IRB approved "honest broker" system?**

* No

[reviewer notes¬]

2.14

Will protected health information from a UPMC/Pitt HIPAA covered entity be accessed for research purposes or will research data be placed in the UPMC/Pitt medical record?

* Yes

If you answer **Yes**, you are required to submit this study to the Research Informatics Office, Health Record Research Request (R3). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted to R3, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS).

Complete the R3 intake form available at http://rio.pitt.edu/services. An R3 representative will conduct a review. You will be notified once your R3 review is complete or if anything further is needed.

Describe the medical record information that will be collected from the UPMC/Pitt HIPAA covered entity and/or the research-derived information that will be placed in the medical records.

This research study may involve the recording of current and/or future identifiable medical information from the hospital and/or other outpatient records. The information that will be recorded will be limited to information concerning diagnosis, age, level of education, past medical and psychiatric history, previous MRI, CT scans, and results of any blood tests. This information will be used for the purpose of identifying whether subjects meet the conditions for participation in this study.

This research study may result in identifiable information that will be placed into medical records held at the UPMC. The nature of the identifiable information resulting from participation in this research study that will be recorded in the medical record includes the results of the MRI or laboratory tests done while participating in the study, that may at a rare instance need to be read for a medical reason (such as abnormal MR or tests).

2.14.1 **Will protected health information from a non-UPMC/Pitt HIPAA covered entity be obtained for research purposes or will research data be placed in the non-UPMC/Pitt medical record?**

* Yes

If Yes, describe how the HIPAA requirements will be met:
In some rare instances, it may be necessary to obtain medical records from a non-UPMC/Pitt hospital stay or PCP's office to ensure the subject meets the inclusion/exclusion criteria for the study. If this is necessary and the case, the research team will have the subject sign a formal HIPAA medical release of information to obtain these records that will then be placed in the research chart with a copy of the signed release of information.

I, Rajesh Narendran , certify that any member of my research team accessing, reviewing and/or recording information from medical records have completed the CITI Privacy & Information Security course or, if completed within the past year, the Internet-Based Studies in Education and Research (ISER) HIPAA for Researchers (Formerly RPF Module 6). The HIPAA certificates must be available for review if audited but do not need to be uploaded into this OSIRIS application.

* Yes

2.14.2

Are you requesting a waiver of the requirement to obtain written HIPAA authorization for the collection of the PHI?

* No

[reviewer notes¬]

2.15 Does this research study involve the long-term storage (banking) of biological specimens?

* Yes

2.15.1

Broadly describe the intended future use of the banked biological specimens:

All blood samples collected during the scan will be stored in a locked freezer at the PET Facility. These samples that will be identified only by a code number will be stored till completion and analysis of all your study results (less than 2 years). Subject identity on these records and any blood samples collected will be indicated by a code rather than by a name. These de-identified blood samples may be sent to outside laboratories that perform specialized analysis (such as cortisol assays).

2.15.2

Indicate the planned length of storage of the banked biological specimens:

* < 2 years

2.15.3 Will biological specimens be stored without identifiers or linkage codes?

* No

[reviewer notes¬]

2.15.4 Will subjects (including family members, if applicable) be informed of their personal results from analyses performed on their biological specimens?

* No

[reviewer notes¬]

2.15.4.1 Justify why the personal results will not be disclosed to the research subjects at this time. Under what conditions, if any, might personal results be disclosed to research subjects in the future?

This is an imaging study in healthy controls to evaluate the feasibility of an imaging paradigm, i.e., can hydrocortisone displace [C-11]NOP-1A binding. There is no such clinical relevance in disclosing the results of these imaging data to the subjects. We do not foresee any condition in which these data will be clinically relevant and warrant disclosure to the subjects.

Note: If the personal results of analyses performed on the banked specimen will not be disclosed to research subjects, the informed consent document corresponding to this research study should address why this information is not being provided. If the personal results of such analyses may be disclosed to research subjects in the future, the conditions for such disclosure should also be addressed in the informed consent form.

[reviewer notes¬]

2.15.4.7 Describe the procedures that will be employed to protect the confidentiality of subjects' private information associated with use of biological specimens:

All biological specimens collected (example, blood samples for cortisol levels, etc.) will be de-identified. Thus, the subjects' information or identifying information will not be compromised.

2.15.4.8 Will the banked biological specimens or data derived from them be provided with subject identifiers to any secondary investigators or external entities?

* No

2.15.4.9 Will research subjects be remunerated in the event of the future commercial development of inventions or products based on the research use of their biological specimens?

* No

[reviewer notes¬]

2.16 Will research participants be asked to provide information about their family members or acquaintances?

* Yes

2.16.1 Describe what information about the third party will be obtained from the participant:

Family Medical and Psychiatric History
Screened subjects will be asked to provide data on family history for medical, psychiatric illness

and drug use disorders. The only information documented is the relationship to the participant and that no names, date of birth or other identifiers will be documented.

2.16.2

If the information about the third party is of a private nature, can the identity of the third party be readily ascertained or associated with this information?

*

No

Describe the **private information** that will be collected and recorded about the third party:
We simply intend to ask information from subjects---medical illness, mental illness and drug and alcohol use in first- and second-degree relatives---to determine items which would be exclusionary for the subject's participation in this study, or related to imaging outcome measures derived in the subject. This information will be no different than the family history obtained during a routine physical and psychiatric exam.

[reviewer notes¬]

2.17 What are the main outcome variables that will be evaluated in this study?

The main outcome measure will be the change in [C-11]NOP-1A VT elicited by hydrocortisone-stimulated CRF (Δ VT). Δ VT will be calculated as the difference between VT measured in the post-hydrocortisone condition and VT measured in the baseline condition on that day (VT BASE), and expressed as a percentage of VT BASE.

2.18 Describe the statistical approaches that will be used to analyze the study data.

* Addressed below:

To determine if [C-11]NOP-1A receptor binding (VT) is increased following the administration of hydrocortisone. This would suggest that there is a compensatory upregulation of NOP receptors to enhance transmission at this site in response to CRF release. Such an interpretation would be consistent with nociceptin, a component of the brain's anti-stress system counteracting CRF, a component of the brain's stress system. The change in [C-11]NOP-1A VT elicited by hydrocortisone-stimulated CRF (Δ VT) will be calculated as the difference between VT measured in the post-hydrocortisone condition and VT measured in the baseline condition on that day (VT BASE), and expressed as a percentage of VT BASE. Scan parameters between baseline and post-hydrocortisone conditions will be performed with paired t-tests. The effect of hydrocortisone on [C-11]NOP-1A VT will be evaluated in the individual ROIs with two tailed paired t-tests. A false discovery rate (FDR) correction with = 0.05 will be applied to correct for multiple comparisons in the ROIs (Benjamini and Hochberg, 1995). Exploratory analyses will be performed using a LMM to evaluate the effects of gender on change in [C-11]NOP-1A VT (Δ VT) elicited by hydrocortisone-stimulated CRF. The effect of hydrocortisone on [C-11]NOP-1A VT in high (e.g., amygdala) and low binding regions (e.g., midbrain, cerebellum) will be contrasted as well. Hydrocortisone-induced changes in clinical variables such as PSS, HAM-A, Heart rate variability, and skin conductance (from E4 wrist band) will also be correlated with the Δ [C-11]NOP-1A VT.

[reviewer notes¬]

2.19

Will this research be conducted in (a) a foreign country and/or (b) at a site (e.g., Navajo Nation) where the cultural background of the subject population differs substantially from that of Pittsburgh and its surrounding communities?

* No

Note that copies of training records, licenses, certificates should be maintained in the study regulatory binder and are subject to audit by the Research Conduct and Compliance Office (RCCO).

In addition, individuals planning to conduct human subject research outside the United States must complete an optional module on the CITI training website: International Studies. Click here to access the instruction sheet for accessing optional CITI modules.

[reviewer notes¬]

2.21

Will this research study be conducted within a nursing home located in Pennsylvania?

* No

Section: Section 3 - Human Subjects

[reviewer notes¬]

Section 3 - Human Subjects

3.1 What is the age range of the subject population?

18-40

3.2 What is their gender?

* Both males and females

Provide a justification if single gender selected:

3.3 Will any racial or ethnic subgroups be explicitly excluded from participation?

* No

If **Yes**, identify subgroups and provide a justification:

3.4 For studies conducted in the U.S., do you expect that all subjects will be able to comprehend English?

* Yes

[reviewer notes¬]

3.5 Participation of Children: Will children less than 18 years of age be studied?

* No

If **No**, provide a justification for excluding children:
Children < 18 years cannot be exposed to radiation the purpose of this study.

[reviewer notes¬]

3.6 Does this research study involve prisoners, or is it anticipated that the research study may involve prisoners?

* No

[reviewer notes¬]

3.7 Will pregnant women be knowingly and purposely included in this research study?

* No

[reviewer notes¬]

3.8 Does this research study involve neonates of uncertain viability or nonviable neonates?

* No

[reviewer notes¬]

3.9 Fetal Tissues: Does this research involve the use of fetal tissues or organs?

* No

[reviewer notes¬]
--->

3.10

What is the total number of subjects to be studied at this site, including subjects to be screened for eligibility?

Note: The number below is calculated by summing the data entered in question 3.11. Any additions or changes to the values entered in 3.11 will be reflected in 3.10.

* 60

3.11

Identify each of the disease or condition specific subgroups (include healthy volunteers, if applicable) that will be studied.

Click on the "Add" button and specify for each subgroup:

1) how many subjects will undergo research related procedures at this site; and

2) if applicable, how many subjects will be required to undergo screening procedures (e.g., blood work, EKG, x-rays, etc.) to establish eligibility. Do Not include subjects who will undergo preliminary telephone screening.

*

	Subgroup	Number to undergo research procedures	Number to undergo screening procedures
View	Healthy controls	20	60

3.12 Provide a statistical justification for the total number of subjects to be enrolled into this research study at the multicenter sites or this site.

* Described below:

No previous [C-11]NOP-1A PET studies have evaluated the effect of hydrocortisone challenge on its binding. To that extent, the studies that are being proposed in this protocol will allow for the computation of effect size and planning for an adequately powered future investigation. In the absence of these data, we used published data from basic investigations to make assumptions for an effect size and power calculations.

In the study by Rodi et al., infusion of 1μg CRF in rodents was associated with a 100% increase in NOP mRNA (Rodi et al., 2008). Based on prior microdialysis studies, we postulate a 2.2-fold increase in amygdala CRF following the 1 mg/kg IV hydrocortisone challenge (Cook, 2002). This is physiologically meaningful because it is in line with increases in amygdala CRF (~1 to 4-fold increase) that have been reported in animal models of addiction (Merlo Pich et al., 1995; Richter et al., 1995; Richter and Weiss, 1999; Richter et al., 2000). However, the exact magnitude that this will translate to increased NOP receptor binding as measured by [C-11]NOP-1A is unknown. Assuming a relatively modest 10% increase in binding to NOP receptors (VT) in response to CRF released by the hydrocortisone challenge, and a 10 - 14% within-subject test-retest variability for [C-11]NOP-1A VT (Lohith et al., 2014), the study is powered at 0.96 to 0.76 to detect an effect at the $p < 0.05$ level using a two tailed paired t test with a sample size of n = 16. It is possible that some subjects may not tolerate the hydrocortisone infusion to complete the PET scans. Thus, we request permission to study an additional 4 subjects, for a total n=20. Note: If we observe an effect on [C-11]NOP-1A VT as reported in Rodi et al. (100% increase in NOP mRNA), the study will be powered at 1.0.

[reviewer notes¬]

3.13 Inclusion Criteria: List the specific criteria for inclusion of potential subjects.

1) Males or females between 18 and 40 years old, of all ethnic and racial origins.

3.14 Exclusion Criteria: List the specific criteria for exclusion of potential subjects from participation.

(1) Current DSM-5 psychiatric disorders including tobacco, alcohol and substance use disorders; and no past history of treatment of DSM5 disorders (SCID screening modules).
(2) History of binge drinking as defined in NIAAA criteria in the past month (http://www.niaaa.nih.gov/alcohol-health/). NIAAA defines "binge drinking" as a pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08 g/dL. This typically occurs after 4 drinks for women and 5 drinks for men—in about 2 hours;
(3) Recreational abuse of opiates, sedative-hypnotics, cocaine, amphetamines, MDMA, and PCP, as well as cannabis use (urine drug screen on PET day, and screening day);
(4) Currently on any prescription medical or psychotropic medication;
(5) Current or past severe medical, endocrine, cardiovascular, immunological or neurological illnesses as assessed by a complete medical history, physical and lab work;
(6) Currently pregnant or breast-feeding;
(7) History of radioactivity exposure via prior nuclear medicine studies or occupational exposure in past twelve months;

(8) Metallic objects in the body that are contraindicated for MRI;
(9) First-degree relative with psychosis or mood or anxiety disorders (due to risk for hydrocortisone to trigger such symptoms).

3.15

Will HIV serostatus be evaluated specifically for the purpose of participation in this research study?

* No

If **Yes**, provide a justification:

	Section: Section 4 - Recruitment and Informed Consent Procedures

[reviewer notes¬]

4.1 Select all recruitment methods to be used to identify potential subjects:
Other Strategies: Described below

4.2

Provide a detailed description of your recruitment methods, including identifying and initiating contact with participants:

Individuals who participate in this study will be recruited via IRB: PRO07080146 (Title: Healthy subjects participating in the screening procedures for positron emission tomography (PET) imaging studies; PI: Dr. Narendran). Interested healthy subjects who contact us for other PMIP research protocols may also be offered this study. These subjects will be consented directly into this study, and undergo screening procedures listed in 2.5.

PRO07080146 is a healthy control screening protocol that establishes minimal eligibility from a medical and psychiatric standpoint. It screens prospective individuals for psychiatric, addictive disorders and medical problems prior to enrolling them into PET research protocols.

Detailed screening and recruitment methods are in PRO7080146:
Briefly, PRO07080146 contains advertisements, to recruit subjects in age range 18-55 years old. However, only subjects who fit the age range for this particular study, 18-40 years old, will be enrolled. Subjects, who are typically enrolled in PRO7080146, are interested in a PET research study and have given us permission to contact them about PET studies. We typically invite them to schedule them via phone--subjects are notified that we have a study they may be appropriate for, and if they are willing to come in to consent for this study with the PI (Note: There is no specific script involved or letters sent out because subjects are only provided with details of the study they are eligible for in person by the PI). If agreeable, they are consented in an in-person interview.

Note: Questions jump from 4.2 to 4.6 as questions 4.3-4.5 have been removed and the information is now captured in 4.1

[reviewer notes¬]

4.6 **Are you requesting a <u>waiver to document</u> informed consent for any or all participants, for any or all procedures? (e.g., a verbal or computerized consent**

script will be used, but the subjects will not be required to sign a written informed consent document. ***This is not a waiver to obtain consent.***

* No

[reviewer notes¬]

4.7 Are you requesting a waiver to obtain informed consent or an alteration of the informed consent process for any of the following?

* Yes

4.7.1 If Yes, select the reason(s) for your request:

Review of identifiable medical records and/or specimens

General Requirements: The Federal Policy **[45 CFR 46.116 (d)]** specifies in order for a waiver of consent to be approved, the request must meet four criteria. For each request, you will be asked to provide a justification addressing how each of these criterion is met.

Review of identifiable medical records: [Note: A waiver of HIPAA Authorization must be requested (2.14.2)] **Include the approximate number of medical records and/or specimens that will be accessed and enter -1 in question 3.11 for the number of subjects to be enrolled.**

The research involves no more than minimal risk to the subjects; **[45 CFR 46.116 (d)(1)]**	Evaluating the potential subjects' medical records to see if they meet any exclusions, for example a prior MRI scans, or Orbital X-ray scan to rule out metal in their eye.
The waiver or alteration will not adversely affect the rights and welfare of the subjects; **[45 CFR 46.116 (d)(2)]**	Because all subjects are healthy controls, the review of their medical records for minimum eligibility will not be exclusionary.
The research could not practicably be carried out without the waiver or alteration; **[45 CFR 46.116 (d)(3)]**	If subjects cannot confirm certain inclusion/exclusions, for example prior radiation exposure in a research study, or lack of metal in eyes in a welder, they will not be able to participate in the study.
	Yes, if there are concerns, subjects will be provided with

Whenever appropriate, the subjects will be provided with additional pertinent information after participation. **[45 CFR 46.116 (d)(4)]**	additional pertinent information after participation.

4.7.2 Under what circumstances (if any) will you obtain consent from some of these subjects?

If a subject's information cannot be confirmed by a simple medical record review, we will seek formal consent (for example, need to talk to their primary care physician about whether they have been exposed to metal/radiation).

[reviewer notes¬]

4.8

Are you requesting an exception to the requirement to obtain informed consent for research involving the evaluation of an 'emergency' procedure?

Note: This exception allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent.

* No

[reviewer notes¬]

4.9

Upload all consent documents for watermarking:

Draft Consent Forms for editing:

Name	Modified Date
Consent.docx 9.26.2017	9/26/2017 9:19 AM

Approved Consent Form(s):

Name	Modified Date
Consent.docx 9.26.2017	11/16/2018 2:43 PM

[reviewer notes¬]

4.10 Will all potential adult subjects be capable of providing direct consent for study participation?

*
Yes

[reviewer notes¬]

4.11

At what point will you obtain the informed consent of potential research subjects or their authorized representative?

Prior to performing any of the screening procedures

4.11.2

Taking into account the nature of the study and subject population, indicate how the research team will ensure that subjects have sufficient time to decide whether to participate in this study. In addition, describe the steps that will be taken to minimize the possibility of coercion or undue influence.

Subjects will always be assessed by a physician investigator. If the subject is in active treatment with one of the investigators, that particular investigator/co-investigator will not consent the subject. Subjects are typically provided as much time as necessary before they decide to sign the informed consent. They are also informed that they are free to withdraw at any time in the study if they do not feel comfortable undergoing any of the study procedures.

[reviewer notes¬]

4.12 Describe the process that you will employ to ensure the subjects are fully informed about this research study.

* Addressed below:

This description must include the following elements:

- who from the research team will be involved in the consent process (both the discussion and documentation);
- person who will provide consent or permission;
- information communicated; and

- any waiting period between informing the prospective participant about the study and obtaining consent

In addition, address the following if applicable based on your subject population:

- process for child assent and parental permission
  - continued participation if a child subject turns 18 during participation
- process for obtaining proxy consent and assent for decisionally impaired subjects
  - continued participation if subject regains capacity to consent

Informed consent shall be obtained (prior to initiating research procedures) by the PI, by a physician co-investigator. The physician co-investigators will be educated in the research procedures related to imaging studies, and trained and supervised by Dr. Narendran prior to conducting the informed consent process by themselves (Study PI).

All risks and benefits of the study will be discussed and reviewed with the subject. The subject will be given as much time as needed to review the consent form, ask questions, and discuss the study procedures with the study physician. The investigator will gauge the subject's understanding of the study procedures through direct questioning of the potential subject about said procedures. The investigator, co-investigator will then obtain written informed consent.

4.13

Are you requesting an exception to either IRB policy related to the informed consent process?

- For studies involving a drug, device or surgical procedures, a *licensed physician who is a listed investigator* is required to obtain the written informed consent unless an exception to this policy has been approved by the IRB
- For all other studies, a *listed* investigator is required to obtain consent (Note: In order to request an exception to this policy, the study must be minimal risk)

* No

If **Yes**, provide a justification and describe the qualifications of the individual who will obtain consent:

4.14 **Will you inform research subjects about the outcome of this research study following its completion?**

* No

If **Yes**, describe the process to inform subjects of the results:

Section: Section 5 - Potential Risks and Benefits

[reviewer notes¬]

5.1

Describe potential risks (physical, psychological, social, legal, economic or other) associated with screening procedures, research interventions/interactions, and follow-up/monitoring procedures performed specifically for this study:

*

View

Research Activity:	Arterial Catheterization
Common Risks:	Complications resulting from such short-term arterial catheterizations infrequently include bleeding, occlusion, or clotting. Incidence of complication increases with the duration of catheterization and are rare when catheters remained in place less than 4 days. Sixteen investigators followed 106 subjects who had arterial lines placed in the context of a PET study (Jons et al 1997). Abnormalities were reported in 8 of 106 (7.5%) cases, all of which were benign and did not require further medical attention. They included redness over the puncture site with pain (n = 1), hematoma (n=2), swelling over the puncture site (n = 2), slow radial and ulnar capillary refill (n = 2, one also had associated cold temperature in the territories of these arteries, however both were within normal limits), index finger contraction (n = 1; causal relationship unclear). Of these eight cases, three (37.5%) were inpatients diagnosed with anorexia nervosa, a condition that may represent a risk factor. All abnormalities were benign, did not affect motor function, and did not require medical intervention.
Infrequent Risks:	We make every effort to minimize participant risk by ensuring that all arterial catheterizations will be performed by qualified anesthesiologists. There is an even more rare risk of cutting off circulation to the hand with arterial catheters, which could result in the need for surgical repair or, in rare instances, could result in the loss of use of part or all of the hand. These complications are rare and usually occur in medically ill patients who have catheters in their wrists for several days. In the proposed study, arterial catheters will remain in place no more than 8 hours.
Other Risks:	*No Value Entered*

View

Research Activity:	Blood Sampling
Common Risks:	Slight bruising, bleeding, soreness, dizziness, and fainting when drawing blood.
Infrequent Risks:	Infection.
Other Risks:	Thrombosis.

View

Research Activity:	Interview and Questionnaires (SCID, Rating Scales)
Common Risks:	The only infrequent risk (expected to occur in 1-10 out of 100) from these questions is that sometimes people can feel uncomfortable about discussing their personal issues.
Infrequent Risks:	*No Value Entered*

	Other Risks:	*No Value Entered*

View	**Research Activity:**	Risk of [C-11]NOP-1A Exposure
	Common Risks:	Adverse reactions to the [C-11]NOP-1A doses used in this study have not been reported.
	Infrequent Risks:	However, the possibility exists for a rare allergic reaction, which may include rash, shortness of breath, and itching to [C-11]NOP-1A to which the participant will be exposed. A physician or RN will therefore be available at all times during the study and an emergency cart will be in close proximity. Other physical risks involve possible (10-25 out of 100 people) muscle aches from lying still for 3 hours or more. If adverse effects would occur that require medical intervention, this is furnished by UPMC.
	Other Risks:	*No Value Entered*

View	**Research Activity:**	Risk of Breach of Confidentiality
	Common Risks:	*No Value Entered*
	Infrequent Risks:	Breach of confidentiality could impact future insurability, employability, etc.
	Other Risks:	Since this is a single-site, open study with a relatively small number of subjects, the data and safety monitoring plan will be implemented using close monitoring of individual subjects by a single individual (the PI). The PI or co-investigators are in daily contact with the research staff who test the participants, score and enter the data and will monitor their procedures to ensure that confidentiality is maintained. We will do everything in our power to protect confidentiality. Information gathered as part of the study including all research records in locked files, and the identity of all specimens and medical information by a research record number, rather than by the subject's name or social security number.

View	**Research Activity:**	Risk of Hydrocortisone
	Common Risks:	Headache, nausea, vomiting, dizziness, insomnia, restlessness, depression, anxiety, unusual moods, increased sweating, increased hair growth, reddened face, thinned skin, easy bruising, tiny purple spots, and irregular menstrual periods. Typically, these side effects are not bothersome and are reversible with time.
	Infrequent Risks:	Other rare, but serious adverse events reported in "medially ill individuals" include anaphylaxis, bradycardia, cardiac arrest, dermatitis, decreased carbohydrate and glucose tolerance, fluid retention, abdominal distention, bowel/bladder dysfunction, negative nitrogen balance, aseptic necrosis of femoral and humeral heads, convulsions, emotional instability, exophthalmoses, glaucoma.
	Other Risks:	It is also possible that hydrocortisone may interfere with the intended effects of vaccination or can increase their risk when exposed to fungal or viral infections.

	Research Activity:	Risk of Lidocaine

View

Common Risks:	The use of Lidocaine may result in mild reactions, including a metallic taste, ringing in the ear.
Infrequent Risks:	Allergic reaction, which may include shortness of breath, itching, rashes, etc.
Other Risks:	*No Value Entered*

View

Research Activity:	Risk of Lorazepam
Common Risks:	Sedation.
Infrequent Risks:	Dizziness, weakness, unsteady gait.
Other Risks:	Serious allergic reaction, which may include rash, itching, swelling, severe dizziness, trouble breathing.

View

Research Activity:	Risk of MRI
Common Risks:	There is a substantial risk (more than 25 out of 100 people) to persons who have metallic objects inside their bodies, as the magnet in the MR scanner can cause these to move. Consequently, participants with pacemakers or metallic objects located in the eye, ear, brain or blood vessel walls will be excluded.
Infrequent Risks:	There is an infrequent risk (1-10 out of 100 people) of heart rhythm disturbances in patients who have previous heart rhythm abnormalities. These subjects will be excluded as well. Women who are pregnant should not undergo MRI because of the possible harmful effects to the fetus. These subjects will be excluded. People with claustrophobia may find this procedure uncomfortable. Participants who developed claustrophobic anxiety during scanning found that this fear dissipated within 15 min while remaining in the scanner, or as necessary, after exiting the scanner. Should the participant develop claustrophobic feelings during the study, or for any reason cannot endure remaining in the scanner, the study will be stopped and the participant will be removed from the scanner.
Other Risks:	*No Value Entered*

View

Research Activity:	Risk of Radiation Exposure
Common Risks:	*No Value Entered*
Infrequent Risks:	*No Value Entered*
Other Risks:	Participation in this research study will involve exposure to radiation associated with the low-dose CT scans and the administration of [C-11]NOP-1A. If participants undergo 2 low-dose CT scans and two injections (12 mCi/injection) of [C-11]NOP-1A, the total radiation exposure will be equivalent to a uniform whole body dose of 0.42 rem (less than 10 % or approximately 1/10th of the annual whole body radiation exposure of 5 rems permissible to radiation workers by federal guidelines). Each additional low-dose CT scan, if required, will result in a uniform whole body radiation dose of about 0.016 rem. This radiation dose is not expected to produce any harmful effects, although there is no known minimum level of radiation exposure considered to be totally free of the risk of causing genetic defects or cancer. The risk associated with the amount of radiation exposure participants receive

	in this study is considered low and comparable to every day risks. No PET studies will be performed on pregnant or potentially pregnant women, as confirmed by pregnancy testing performed at screening and prior to each PET scanning session. In order to limit the amount of radiation exposure received by research subjects, all individuals currently exposed to radiation in the workplace are excluded, as well as individuals who have participated in radioactive drug studies during the previous year wherein the total cumulative annual radiation dose (i.e., from participation in the previous radioactive drug study [studies] and this study) would exceed the radiation dose limits specified in the FDA regulations (i.e., 21 CFR 361.1) that govern the research use of [C-11]NOP-1A in this study.

View

Research Activity:	Venous Catheterization
Common Risks:	*No Value Entered*
Infrequent Risks:	Insertion of a catheter for intravenous injection of the PET radiopharmaceutical is rarely associated with the chance of infection (less than 1 out of 100 people), but more commonly associated with slight pain, bruising, bleeding or soreness at the puncture site (10-25 out of 100 people).
Other Risks:	*No Value Entered*

5.1.1 Describe the steps that will be taken to prevent or to minimize the severity of the potential risks:

1. Risk of Arterial Catheterization
The arterial catheterization risks will be minimized, prior to the procedure, as each participant will undergo an Allen's test to ensure competency of collateral arterial circulation. Lidocaine may be used to reduce the pain during arterial catheterization and there is a rare (less than 1 out of 100 people) risk of allergic reaction, which could rarely (less than 1 out of 100 people) be life-threatening, to the Lidocaine. Further, we will make every effort to minimize participant risk by ensuring that all arterial catheterizations will be performed by qualified anesthesiologists. Indeed, this is our routine practice in the UPMC PUH PET Facility and we have an excellent safety record. Specifically, we have performed over 1000 arterial catheterizations for PET research studies from 1996 through September 2002 with no serious complications, such as ischemia, irreversible injury, infection or other serious problems. Experienced medical personnel will perform all catheter placements and a fully equipped medical cart is located in the PET Facility.

2. Risk of Blood Sampling/Loss
Adverse effects of blood sampling will be minimized by exclusion of subjects with low hemoglobin levels during screening.

3. Risk of Interview and Questionnaires
Only trained clinical research coordinators will perform these rating scales. These coordinators are supervised by PMIP program manager, Ms. Jennifer Paris, who is a certified LPC (licensed psychology counselor). Participants experiencing anxiety or tearfulness during the psychological assessments will be reassured that they are just there to do their best and it does not matter how well they score. They will be encouraged to continue, but allowed to stop if they feel too

distressed.

4. Risk of Adverse Reaction from [C-11]NOP-1A
Adverse reactions to the [C-11]NOP-1A dosage used in this study have not been reported. However, the possibility exists for a rare (1 out of 100 people) reaction to any of the drugs or procedures to which the participant will be exposed. A physician will be available during the study and an emergency cart will be in close proximity.

5. Risk of Breach of Confidentiality
We will do everything in our power to protect confidentiality. Information gathered as part of the study including all research records in locked files, all specimens and medical information are identified by a research record number, rather than by the subject's name or social security number.

6. Risk of Lidocaine
Subjects will be asked if they are allergic to Lidocaine or Novocain, commonly used in dental procedures, in order to minimize the risk of a serious allergic reaction.

7. Risk of MRI
The MR scan risks will be minimized by thorough participant screening. The PI, research team and MRI technicians will ask the participant a list of questions about previous activities that could potentially put them at risk for having metal in their body. If there is a possibility of metal being present in the participant's body, the participant will be excluded from the study protocol.

8. Risk of Radiation Exposure
In order to limit the amount of radiation exposure received by research subjects, all individuals currently exposed to radiation in the workplace are excluded, as well as individuals who have participated in radioactive drug studies during the previous year wherein the total cumulative annual radiation dose (i.e., from participation in the previous radioactive drug study [studies] and this study) would exceed the radiation dose limits specified in the FDA regulations (i.e., 21 CFR 361.1) that govern the research use of [C-11]NOP-1A in this study.

9. Venous Catheterization
Risks of venous catheterization will be minimized by utilizing trained personal to insert the catheter.

10. Risk of Hydrocortisone
The proposed dose of hydrocortisone (1mg/kg, IV, i.e., ≤ 100 mg) in this study is far below the FDA approved maximum IV dose of 500 mg. This will reduce the risk of these serious adverse effects. Furthermore, IV hydrocortisone has been administered to healthy humans at doses ≤ 200 mg with no serious side effects in several previous research studies (Jung et al., 2014; Symonds et al., 2012; Wachtel et al., 2001; Wachtel and de Wit, 2001).

Specific measures and precautions to prevent medical and psychiatric effects:
Subjects will be screened for absence of significant past and current medical conditions with a complete medical history, physical examination, routine blood tests (that will include CBC with differential counts, electrolytes, liver, thyroid, adrenal, kidney function tests, and creatine kinase) urine toxicology and EKG. They will be excluded if they have any history of cardiovascular disease, arrhythmias, or an abnormal EKG. In addition, subjects with a prior or current history of immune-compromise, HPA-axis dysfunction, Cushing's syndrome, obesity, hyperglycemia, hyperlipidemia, cataracts, glaucoma, and osteoporosis will be excluded. Finally, subjects with a family history for mood, anxiety and psychotic disorder will be excluded as well.

The study will be cancelled if the subject has a blood pressure < 90/60 or > 150/90.

During and after the hydrocortisone administration, subjects will be under constant monitoring for serious adverse events (including anaphylaxis, bradycardia, etc.). Administration of hydrocortisone will take place in the presence of a physician. A twelve lead EKG, a code cart, and defibrillator are available in the room in case of complications. If there is a drop in blood pressure, IV fluids will be used to control the blood pressure response. In case of chest pain, chest tightness or other symptoms suggestive of cardiac ischemia, the experiment will be canceled and a twelve lead EKG will be immediately obtained to rule out angina (ST segment elevation or depression as compared to the baseline EKG) or arrhythmia. If serious medical signs and symptoms persist > 10 minutes, the subjects will be taken to the UPMC Presbyterian ER for further medical treatment. If psychiatric signs and symptoms persist > 10 minutes (example, depression, anxiety, etc.), the subjects will be managed by the PI (starting with re-assurance, and if need oral lorazepam 1-2 may be administered). If these symptoms persist and are a cause for a concern then a referral will be made to a higher level of care, example WPIC psychiatric emergency room. All subjects who receive hydrocortisone will be monitored for a minimum of 6 hours in the PET facility, following hydrocortisone administration. Subjects will be evaluated by a physician and discharged home only if they meet the following criteria: (a) a blood pressure of > 90/60 and < 150/90 (b) a heart rate > 50 or < 110 (c) no reported subjective or objective side effects from the hydrocortisone at discharge (d) a normal EKG (or not clinically significant, or no change from baseline as determined by a physician) (e) a normal physical exam (f) and a normal mental status exam.

5.2 **What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study?**

* **Addressed below:**

If a clinically significant, unexpected disease or condition occurs during the conduct of the study that is directly related to study intervention, it will be evaluated and managed by one the physician investigators. If this event is an emergency, the subject will be taken to the UPMC Presbyterian ER and medical care will be initiated as needed.

5.3 All the risk questions (screening, intervention/interaction, follow-up) have been merged into one question (5.1).

[reviewer notes¬]

5.4 **Do any of the research procedures pose a physical or clinically significant psychological risk to women who are or may be pregnant or to a fetus?**

* Yes

5.4.1 **List the research procedures that pose a risk to pregnant women or fetuses:**

Exposure to radiation can lead to abnormal fetal development.

5.4.2 **Describe the steps that will be taken to rule out pregnancy prior to exposing women of child-bearing potential to the research procedures that pose a risk to pregnant women or fetuses:**

A urine pregnancy test will be performed on all women of child-bearing potential on the day of,

and prior to, the PET scanning procedures.

5.4.3

Describe the measures to prevent pregnancy, and their required duration of use, that will be discussed with women of child-bearing potential during and following exposure to research procedures:

1. Subjects will receive a blood pregnancy test at screening.
2. A urine pregnancy test will be performed on all women of child-bearing potential on the day of, and prior to, the PET scanning procedures.
3. In addition, all female subjects will be educated and instructed to use contraception two-weeks prior to undergoing any of the radiation related procedures. A confirmation of their use of protection is documented in the case report form.

[reviewer notes¬]

5.5 **Do any of the research procedures pose a potential risk of causing genetic mutations that could lead to birth defects?**

* Possibly or Definitely

5.5.1

List the research procedures that pose a potential risk of genetic mutations/birth defects:

Exposure to radiation can lead to abnormal fetal development.

5.5.2

Describe the measures to prevent pregnancy, and their required duration of use, in female subjects and female partners of male subjects during and following exposure to research procedures:

1. Subjects will receive a blood pregnancy test at screening.
2. A urine pregnancy test will be performed on all women of child-bearing potential on the day of, and prior to, the PET scanning procedures.
3. In addition, all female subjects will be educated and instructed to use contraception two-weeks prior to undergoing any of the radiation related procedures. A confirmation of their use of protection is documented in the case report form.

[reviewer notes¬]

5.6

Are there any alternative procedures or courses of treatment which may be of benefit to the subject if they choose not to participate in this study?

* Not applicable

If **Yes**, describe in detail:

[reviewer notes¬]

5.7

Describe the specific endpoints (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression) or other circumstances (e.g., subject's failure to follow study procedures) that will result in discontinuing a subject's participation?

* Describe below:

Subjects will be withdrawn from the study at their request or by the determination of the study physician. Reasons could include experiencing claustrophobia during the MRI or PET scan, or experiencing adverse effects from hydrocortisone, or [C-11]NOP-1A, failure of adherence to research protocol.

[reviewer notes¬]

5.8

Will any individuals <u>other</u> than the investigators/research staff involved in the conduct of this research study and authorized representatives of the University Research Conduct and Compliance Office (RCCO) be permitted access to research data/documents (including medical record information) associated with the conduct of this research study?

* Yes

5.8.1

Identify the 'external' persons or entity who may have access to research data/documents and the purpose of this access:

Other research investigators interested in this topic may be provided access to the de-identified data for data pooling and replication of these data.

5.8.2

Will these 'external' persons or entity have access to identifiable research data/documents?

*

No; the research data/documents will be coded and subject identifiers removed prior to access by the external persons

If **Yes**, describe how they will protect the confidentiality of the research data:

5.9

Has or will a Federal Certificate of Confidentiality be obtained for this research study?

* No

5.10

Question has been moved to 5.17

5.11

Question has been moved to 5.16

[reviewer notes¬]

5.12 **Does participation in this research study offer the potential for direct benefit to the research subjects?**

No - Describe the general benefits to society (e.g., increased knowledge; improved safety; better health; technological advancement) that may result from the conduct of this research study.

Describe the benefit:
The general benefits to society from this particular research protocol include gaining a better understanding of the effect of nociceptin-corticotrophin interactions. It is possible that future studies using this paradigm may detect that this interaction is abnormal in addictive and psychiatric disorders, and lead to better treatments.

5.13 **Describe the data and safety monitoring plan associated with this study. If the research study involves multiple sites, the plan must address both a local and central review process.**

The study results will be monitored on a bi-monthly basis to ensure appropriate data collection and study procedures justify the continuation of the study. The PI will ensure that the IRB, and when applicable (i.e., if felt to be related to administration of a radioactive drug) the RDRC, is immediately notified of any adverse event. Dr. Narendran is routinely notified of any medical concerns during the conduct of the study. The PET methodology, including the arterial blood draw procedure, is reviewed at least monthly to ensure that risk is minimized and participant comfort maximized. Expected and unexpected serious (including fatal) adverse reactions and major unresolved disputes between the research investigator(s) and the research participant or between research investigator(s) will be expeditiously reported to the IRB and, when applicable (i.e., if felt to be related to administration of a radioactive drug) the RDRC as per Chapter 3, Section 3.3 of the IRB reference manual. At the time of renewal, the IRB will be provided with a summary indicating the frequency of the monitoring, cumulative adverse event data, information regarding participant safety or ethics changes, confidentiality issues, benefit-to-risk changes and recommendations on continuing, changing or terminating the study. None of the investigators have a conflict of interest with the radiotracer ([C-11]NOP-1A) or hydrocortisone being used in this study.

[reviewer notes¬]

Section 5 - Potential Risks and Benefits of Study Participation

5.14

What precautions will be used to ensure subject privacy is respected? (e.g. the research intervention will be conducted in a private room; the collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe)

1) All research intervention will be conducted in a private room.
2) The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.
3) Drapes or other barriers will be used for subjects who are required to disrobe for procedures, such as EKG, etc.

5.15

What precautions will be used to maintain the confidentiality of identifiable information? (e.g., paper-based records will be kept in a secure location and only be accessible to personnel involved in the study, computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information, whenever feasible, identifiers will be removed from study-related information, precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys, audio and/or video recordings of subjects will be transcribed and then destroyed to eliminate audible identification of subjects)

1) To minimize these risks, a study code number will be assigned and no subject will be identified by name. This will ensure subject confidentiality. The study code will be used to identify all data. The code containing the subject's name and number will be kept secure by the Study Investigator in a password protected electronic database behind UPMC firewall at PET Facility. All the investigator's research personnel will be allowed access to information on a need to know basis only.
2) All data collected will be kept in locked file cabinets in a locked and secured area.
3) All imaging data stored in electronic archives such as computers are de-identified, password protected and/or stored on the PET/MR imaging facility servers that are behind a UPMC Fire wall. Images that are acquired do not typically have any identifying data of the subjects entered. They are de-identified by the technician and assigned a code--the link between this code and imaging data files are maintained in a protected PET facility database.

5.16

If the subject withdraws from the study, describe what, if anything, will happen to the subject's research data or biological specimens.

If the subject withdraws from the study their clinical and imaging data will be de-identified. These de-identified data that was collected up until the time they withdrew consent may continued to be cited in analysis and/or publications with reasons for withdrawal of consent . Biological specimens such as blood samples that are stored for future analysis will be destroyed after the subject withdraws consent because there is no use for them unless the subject completes the entire imaging protocol.

5.17

Following the required data retention period, describe the procedures utilized to protect subject confidentiality. (e.g., destruction of research records; removal of identifiers; destruction of linkage code information; secured long-term retention)

All research records will be kept in locked, secured facilities for at least 7 years or until the investigators have completed analyzing and publishing the data, whichever occurs later. After that time, data will be secured for long-term retention (this will include PET and MRI images that will be archived in the PET Facility servers).

Section: Section 6 - Costs and Payments

[reviewer notes¬]

6.1 **Will research subjects or their insurance providers be charged for any of the procedures (e.g., screening procedures, research procedures, follow-up procedures) performed for the purpose of this research study?** *

No

[reviewer notes¬]

6.2 **Will subjects be compensated in any way for their participation in this research study?**

* Yes

6.2.1 **Describe the amount of payment or other remuneration offered for complete participation in this research study.**

Healthy Control Participants (HC) will be paid up to $1100 for their participation in this protocol.

6.2.2 **Describe the amount and term of payment or other remuneration that will be provided for partial completion of this research study.**

Healthy Control Participants (payment breakdown for the total of $1100)
1) One hundred dollars ($100.00) will be paid for completing all listed screening procedures (SCID, psychiatric rating scales, physical exam, blood work);
2) Fifty dollars ($50.00) will be paid for completion of the structural MRI scan;
3) One hundred dollars ($100.00) for the arterial line;
4) Two hundred and fifty dollars ($250.00) for completion of each [C-11]NOP-1A PET scan ($250.00 x2 =$500);
5) One hundred and fifty ($150.00) for completion of the hydrocortisone challenge;
6) Two hundred dollars ($200.00) bonus for completion of all the above listed procedures.

In addition, any parking fees or transportation costs related to participation in this study will be reimbursed.

	Section: Section 7 - Qualifications and Source(s) of Support

[reviewer notes¬]

7.1

Summarize the qualifications and expertise of the principal investigator and listed co-investigators to perform the procedures outlined in this research study.

Rajesh Narendran, M.D. is an Associate Professor in Radiology and Psychiatry. Dr. Narendran completed a schizophrenia research fellowship at Columbia University, NY, NY prior to coming to the University of Pittsburgh. He has extensive experience in PET imaging of brain receptors in humans. He is currently a research psychiatrist at the University of Pittsburgh PET Facility. Dr. Narendran is also a fully licensed PA physician and a board-certified psychiatrist who treats drug/alcohol addicted and psychiatric patients at the UPMC WPIC re:solve crisis center. He has 15+ years of experience in clinical psychiatry and continues to be active in clinical practice. Since 2001, he has published numerous clinical research studies in cocaine use disorder and alcoholism in leading clinical psychiatric journals, such as American Journal of Psychiatry and Biological Psychiatry.

N. Scott Mason, Ph.D. is an Associate Professor of Radiology. Dr. Mason has research interests in the development and application of radiosynthetic methods in the development of PET radioligands for the various receptor systems. Recent efforts have included the development of radioligands for use in PET oncology applications, as well as the application of PET in the area of developmental biology. He will be responsible for the production and quality control of [C-11]NOP-1A.

James M. Mountz, M.D., Ph.D. is a Professor of Radiology, Division of Nuclear Medicine, and Director of NeuroNuclear Medicine. He has been involved in imaging and stroke rehabilitation for over 20 years.

[reviewer notes¬]

7.2 **Indicate all sources of support for this research study.**

*

Selections
Federal: Upload a copy of the entire grant application **(including the cover sheet)** if our site is the awardee institution; for federal contracts, upload a copy of the research plan

If **Federal** support, provide the sponsor information:

	Federal sponsor	Grant Title	Grant number	Awardee institution	Federal grant application
View	NIH/NIDA	In vivo imaging of corticotropin releasing factor-nociceptin receptor interactions	DA042633	Univ of Pittsburgh	R21 DA042633.pdf(0.01)

For projects not supported by a federal grant, upload the research plan that was submitted for funding:

Name Modified Date

If **Industry** support, provide the sponsor information and level of support:

If **Foundation** support, provide the sponsor information:

If **Other** support, provide the support information and level of support:

[reviewer notes¬]

7.3

Is this study funded in part or whole by a PHS Agency?

* Yes

Does any investigator* involved in this study (select all that apply):

	Name
☐	**A.** Have a financial interest (aggregated value of equity and remuneration** during the past or next twelve months) in a **publicly-traded entity** that either sponsors*** this research or owns the technology being evaluated or developed that exceeds **$5,000 but not $10,000**?
☐	**B.** Have a financial interest (aggregated value of equity and remuneration during the past or next twelve months) in a **publicly-traded entity** that either sponsors this research or owns the technology being evaluated or developed that exceeds **$10,000**?
☐	**C.** Receive remuneration (during the past or next twelve months) from a **non-publicly traded entity** that either sponsors this research or owns the technology being evaluated or developed that exceeds **$5,000 but not $10,000**?
☐	**D.** Receive remuneration (during the past or next twelve months) from a **non-publicly traded entity** that either sponsors this research or owns the technology being evaluated or developed that exceeds **$10,000**?
☐	**E.** Have equity in a **non-publicly traded entity** that either sponsors this research or owns the technology being evaluated or developed?
☐	**F.** Receive reimbursement or sponsorship of travel expenses (for one trip or a series of trips during the past or next twelve months) by an outside entity that either sponsors this research or owns the technology being evaluated or developed that exceeds **$5,000**?
☐	**G.** Have rights as either the author or inventor of **intellectual property** being evaluated or developed in this research that is the subject of an issued patent or has been optioned or licensed to an entity?
☐	**H.** Have an officer or management position**** with a **Licensed Start-up Company** overseen by the COI Committee that either sponsors this research or owns the technology being evaluated or developed?
	I. Receive compensation of any amount when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater

- [ ] for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?

- [x] **None of the above options apply and there are no other financial conflicts of interest in the conduct of this research.**

***Investigator** means the PI, co-investigators, and any other member of the study team, regardless of title, who participates in the design, conduct, or reporting of this research, as well as his/her spouse, registered domestic partner, dependents, or other members of his/her household. **The PI is responsible for ensuring that s/he and all other relevant members of the study team review the above questions describing Significant Financial Interests.**

****such as salary, consulting fees, honoraria, or paid authorship

*****through the provision of funds, drugs, devices, or other support for this research

******Such as serving on the Board of Directors or Board of Managers or a position that carries a fiduciary responsibility to the company (e.g., CEO, CFO, CTO, or CMO).

Section: Supporting Documentation

[reviewer notes¬]

Supporting Documentation Section

References and Other Attachments

Additional documents:

Name	Modified Date	Version
Data security form	7/26/2016 4:28 PM	0.01
R21 DA042633.pdf	3/11/2016 3:38 PM	0.01
References.pdf	3/11/2016 3:40 PM	0.01

Please use the Add button to the left to upload additional documents if needed.

[reviewer notes¬]

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

"Applicable clinical trials" are required **by federal law** to be registered in ClinicalTrials.gov.

Applicable Clinical Trials (ACTs) are studies that meet the following criteria:

- The study is an interventional study AND
- The study intervention is a drug, biologic, medical device, radiation or genetic AND
- The Study is not Phase 0 or 1 AND
- The study has at least one site in the United States or is conducted under an investigational new drug application or investigational device exemption

NIH Policy

Effective January 18, 2017, revised NIH Policy requires that all clinical trials funded in whole or in part by the NIH be registered and results information posted on ClinicalTrials.gov.

As defined by the NIH, a clinical trial is:

> *A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health related biomedical or behavioral outcomes.*

The NIH Policy extends beyond the Food and Drug Administration Amendment Act (FDAAA 801) requirements in that it requires registration and results reporting of:

- clinical trials of behavioral, surgical and other types of health and medical interventions

- phase 1 studies of drugs and biological products
- small feasibility studies of device products

Failure to submit all required registration and results information requested on ClinicalTrials.gov can jeopardize University grant funding, the future funding of the grantee and subject the University of Pittsburgh to future monetary penalties.

In addition, to promote transparency of the clinical trials process, the International Committee of Medical Journal Editors (ICMJE) has established a policy requiring the entry of clinical trials in a public registry, such as ClinicalTrials.gov, prior to subject enrollment as a condition of consideration for publication of the trial results.

* **Based on the above information, will this study be registered in ClinicalTrials.gov?**
Yes

Who will serve as the Responsible Party? UPMC/Pitt Investigator or IND/IDE Pitt Sponsor

Why are you registering your study? (Check all that apply)

It is strongly encouraged by the NIH

If you are not yet registered and need to establish an account for the PI or other research staff that may need to access the record, please send an email to the University of Pittsburgh PRS administrator at ctgov@pitt.edu with the following information for each individual:

- Full name
- Telephone number
- Pitt or UPMC email address

If you have any questions or concerns, please email us at ctgov@pitt.edu.

To find out additional information about how to register your study go to:
https://www.clinicaltrials.gov/ct2/manage-recs/how-register